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- (54) **Acidic indole compounds and their use as antiallergy agents.**

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Description

The present invention provides novel acidic indole compounds, novel methods for synthesis thereof, selected novel intermediates, pharmaceutical compositions and use of the novel compounds, particularly as antiallergic agents. Additionally, the compounds prevent the release of mediators such as leukotrienes from basophils and neutrophils providing activity useful in cardiovascular disorders as well as in antiinflammatory and antimigraine treatment. See B. Samuelsson, "Leukotrienes: Mediators of Immediate Hypersensitivity Reactions and Inflammation," *Science*, Vol. 220, pp 568 (1983), P. J. Piper, "Leukotrienes," *Trends in Pharmacological Sciences*, pp 75 & 77 (1983), and J. L. Romson, et al; "Reduction of the Extent of Ischemic Myocardial Injury by Neutrophil Depletion in the Dog," *Circulation*, Vol. 67, p 1016 (1983).

European Patent Application 71,935 discloses indole derivatives. However, the novel compounds of the present invention include differences from the compounds in EP 71,935 not suggested by its disclosure.

Furthermore, the antiallergic utility now found for the novel compounds of the present invention is not within the teachings for the indole derivatives disclosed by the EP 71,935 reference.

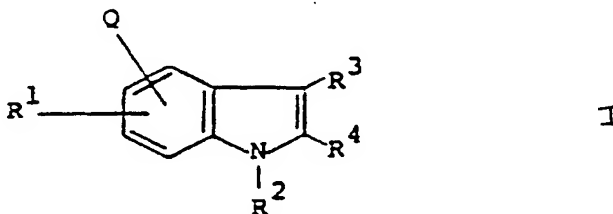
USP 4316904 discloses certain indolopyrone tetrazoles and carboxamidotetrazoles useful as anti-allergic agents.

USP4432986 discloses certain compounds useful as anti-allergic agents formed from carboxamido tetrazoles and dibenzofurans, dibenzothiophenes, naphthalenes and 2,3-ethylene dioxo benzenes.

A vast array of benzofurans and benzothiophenes are disclosed in EP-A-0146243 for use as inhibitors of the mammalian 5-lipoxygenase enzyme system.

Our copending application, EP-A-0187487, discloses certain benzofurans and benzothiophenes having anti-allergy activity.

According to the present invention there is provided a compound of Formula I,



wherein (1) R¹ and Q are independently H, alkyl of from one to twelve carbons, inclusive, alkoxy of from one to twelve carbons, inclusive, mercapto, alkylthio of from one to four carbons, inclusive, alkylsulphinyl of from one to four carbons, inclusive, alkylsulphonyl of from one to four carbons, inclusive, hydroxy, R¹ taken twice having each on adjacent carbons such that the two R's together are methylenedioxy, nitro, amino, substituted amino, or halogen; (2) R² is H, alkyl of from one to twelve carbons, inclusive, phenyl, substituted phenyl or benzyl; (3) R³ is H, alkyl of from one to twelve carbons, inclusive, alkoxy of from one to twelve carbons, inclusive, mercapto, alkylthio of from one to four carbons, inclusive, phenylthio, substituted phenylthio, alkylsulphinyl of from one to four carbons, inclusive, phenylsulphinyl, substituted phenylsulphinyl, alkylsulphonyl of from one to four carbons, inclusive, phenylsulphonyl, substituted phenyl sulphonyl, amino, and substituted amino; and (4) R⁴ is carboxamido tetrazole (A) or tetrazole (B); and pharmaceutically acceptable salts thereof,

[wherein substituted phenyl is a phenyl having one or two substituents selected from alkyl of from one to four carbons inclusive, alkoxy of from one to four carbons inclusive, hydroxy, nitro, amino, mono- or di-alkyl amino wherein alkyl is from one to four carbons, mercapto, alkylthio of from one to four carbons, methylenedioxy, or halogen and

substituted amino is mono- or di-alkyl amino wherein alkyl is from one to four carbons.]

Further, the present invention includes a process for the preparation of a compound of Formula I, wherein R¹, Q, R², R³, and R⁴ are as defined above, which comprises treating a compound having the Formula III, wherein R¹, Q, R², and R³ are as defined above to obtain the compound of Formula I as shown in Scheme I.

The process which comprises treating the compound of Formula III to obtain the compound of Formula I, wherein R⁴ of Formula I is the moiety shown by A comprises contacting the compound of Formula III with the compound of Formula II, in the presence of a coupling agent. See Scheme II.

A compound of Formula III is known or can readily be prepared from compounds known in the literature. For example, compounds of Formula III wherein R^3 is an amino or a substituted amino may be prepared in a manner analogous to or derived from the process described by P. C. Unangst, *J. Heterocyclic Chem.*, Vol. 20, 495 (1983). Unangst describes compounds in which the substituent is an amino. Substituted amino groups can be prepared from the amino compounds by standard methods.

An alternate route to compounds of Formula III having R^3 as amino or substituted amino groups may be analogous to a reaction described by M. A. Khan, et al, in *Chem. Pharm. Bull.*, Vol. 25, 3110 (1977).

Compounds of Formula III wherein R^3 is a mercapto or alkylthio within the present invention is shown or can be made by procedures from analogous compounds to those shown by K. Nagarajan, et al, *Indian J. of Chem.*, Vol. 20B, 672 (1981). Likewise, compounds of Formula III wherein R^3 is alkylsulphinyl or alkylsulphonyl can be prepared by oxidation of the corresponding alkylthio compounds by methods familiar to those skilled in the art.

The process which comprises treating the compound of Formula III to obtain the compound of Formula I₂ wherein R^4 of Formula I is the moiety shown by B is one in which the compound of Formula III is (1) contacted with ammonia and the resulting amide dehydrated to give a compound of Formula IV, wherein R^1 , Q, R^2 , and R^3 are as defined above and (2) the compound of Formula IV is then treated in a manner analogous to that described by the K. Sisido cited reference hereinafter to give the compound of Formula I₂. See Scheme III.

Additionally, the present invention includes a process for the preparation of the compound of Formula I₃ wherein R^1 , Q, and R^2 are as defined above and OR^6 wherein R^6 is benzyl or alkyl of from one to twelve carbons, inclusive, which comprises (1) esterifying a compound of Formula VII, (2) treating the esterification product to obtain a compound of Formula VI by a reaction analogous to that described by K. Sisido, et al, *J. Organometallic Chem.*, Vol. 33, 337 (1971), protecting the compound of Formula VI wherein Y is an appropriate protecting group, and cyclizing the protected compound, and finally, alkylating with a compound $HalR^6$, wherein R^6 is as defined above, and then deprotecting to obtain the compound I₃. Cyclization is accomplished generally by treating the protected compound of Formula VI with potassium butoxide in tetrahydrofuran. See Scheme IV.

Cyclization can also be used to prepare a compound of Formula IV of Scheme III for use as an intermediate in the preparation of compounds of Formula I₃ described above. For example, esterification of a compound of Formula VIII, wherein R^1 and R^2 are as defined above may be followed by cyclization to obtain the compound IV. See Scheme V.

The antiallergy activity of the compounds having the Formula I of the present invention was determined by the well-known Schultz-Dale procedure, that is described in N. Chand, et al, *Agents and Actions*, Vol. 8, 171 (1978), or the Herzheimer in vivo antiallergy test, described in H. Herxheimer, *J. Physiol. (London)* Vol. 117, 251 (1952).

By virtue of this antiallergy activity the compounds of Formula I are useful in treating an allergic hypersensitivity reaction (AHR) having broad symptoms. For example, the symptoms may include dermatitis, lacrimation, nasal discharge, coughing, sneezing, nausea, vomiting, diarrhea, difficulty in breathing, pain, inflammation, and in severe cases, anaphylactic shock, circulatory collapse, and even death. The AHR is found in man as well as other animals suffering from bronchial asthma, seasonal pollinosis (e.g., hayfever), allergic rhinitis, urticaria, allergic conjunctivitis, food allergies, and anaphylactoid reactions.

In an AHR an antibody (reagin in man) influences the cell membrane of a mast cell by reacting with an antigen, to initiate reactions within the mast cell which ultimately causes release of mediators (bioactive compounds) such as bradykinin, slow reacting substance A (SRS-A), histamine, serotonin (5HT), possibly some prostaglandins, or other not now known substances. The mediator is released from the mast cell whereupon it attaches to suitable receptor sites (e.g., on smooth muscle) resulting in AHR attack symptoms. Various methods are used to relieve the symptoms of AHR. It is not known, however, what mechanism is effected for the antiallergic use by the compounds having Formula I of the present inventions.

Pharmaceutical compositions are prepared from compound Formula I and salts thereof described as the present invention having inert pharmaceutical carriers. The compositions may be either solid or liquid.

A physician or veterinarian of ordinary skill readily determines a subject who is exhibiting AHR symptoms. Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically acceptable dosage forms by conventional methods known to the pharmaceutical art.

The compounds can be administered in such oral unit dosage forms such as tablets, capsules, pills, powders, or granules. They also may be administered rectally or vaginally in such forms as suppositories or bougies; they may also be introduced parenterally (e.g., subcutaneously, intravenously, or intramuscularly), using forms known to the pharmaceutical art. They are also introduced directly to an affected area, (e.g., in

the form of eye drops or by inhalation). For the treatment of AHR induced conditions such as erythema, the compounds of the present invention may also be administered topically in the form of ointments, creams or gels. In general, the preferred route of administration is orally.

An effective but nontoxic quantity of the compound is employed in treatment. The ordinarily skilled physician or veterinarian will readily determine and prescribe the effective amount of the anti-AHR agent to prevent or arrest the progress of the condition. In so proceeding, the physician or veterinarian could employ relatively low dosages at first, subsequently increasing the dose until a maximum response is obtained.

Initial dosages of the compounds of the invention having Formula I are ordinarily in the area of 10 mg up to 2 g per day orally, preferably 10 mg to 500 mg per dose orally, given from one to four times daily or as needed. When other forms of administration are employed equivalent doses are administered.

The compounds of this invention can also be administered as pharmacologically acceptable salts such as can be readily prepared with inorganic and organic bases, such as NaOH, KOH, Mg(OH₂), Ca(OH)₂, NH₄OH, substituted ammonium salts, L-arginine, choline and N-methyl glucamine.

The novel compounds of Formula I are named as derivatives of indoles by virtue of a nitrogen containing heterocyclic five-membered ring fused to a phenyl ring. The fused rings are numbered counterclockwise starting with the nitrogen atom at the one position as shown in the ring system of Formula I'.

Certain compounds within the scope of Formula I are preferred, since they have a more advantageous pharmacologic effect. Preferred compounds include compounds of Formula I wherein Q is hydrogen. Compounds of the Formula I more preferred are the following compounds: (1) 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, and (2) 3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

Of the above, the most preferred compound is 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, and its pharmaceutically acceptable salts, eg. its arginate and sodium salts.

Alkyl of from one to four carbons, inclusive, is methyl, ethyl, propyl, butyl, or isomeric forms thereof.

Alkyl of from one to twelve carbons, inclusive, is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, etc, and includes isomeric forms of the alkyl of from one to six carbons, inclusive. Alkyl of from one to six carbons, inclusive, are preferred.

Alkoxy of from one to twelve carbons, inclusive, is methoxy, ethoxy, propoxy, butoxy, etc, and includes isomeric forms of alkoxy of from one to six carbons, inclusive. Alkoxy of from one to six carbons, inclusive, are preferred.

Substituted phenyl is a phenyl having at least one substituent and particularly one or two substituents such as, alkyl of from one to four carbons, inclusive, alkoxy of from one to four carbons, inclusive, hydroxy, nitro, amino, substituted amino, mercapto, alkylthio of from one to four carbons, methylenedioxy, or halogen.

Substituted amino is mono- or di-alkyl amino wherein alkyl is from one to four carbons, inclusive.

Halogen is fluoro, chloro, bromo, iodo, or trifluoromethyl.

The compounds of this invention are synthesized as illustrated in Schemes I-V.

Generally, the compounds having the Formula I, as illustrated in Scheme I are prepared by treating an indole-2-carboxylic acid of Formula III wherein R¹, Q, R², and R³ are as defined above.

A 3-alkoxy ester of Formula IX, wherein R¹, Q, and R² are as defined above, R³ is alkoxy, and R⁵ is benzyl or alkyl of from one to six, inclusive, as shown in Scheme VI may be prepared by methods analogous to those known in the literature. See for example, H. Plieninger, et al, *Chem. Ber.*, Vol. 104, 1863 (1971), and J. Galun, et al, *J. Heterocyclic Chem.*, Vol. 16, 221 (1979). If R³ is hydroxy in the compound of Formula IX it must be protected by, for example, treatment with a compound of Formula R⁶X wherein R⁶ is alkyl of from one to six carbons, inclusive, or benzyl and X is halogen, sulfonate or the like using conditions analogous to those known in the art. Protection of other R¹, Q, R², or R³ groups is also readily understood by those skilled in the art.

The 3-alkoxy ester is then converted to carboxylic acids of Formula III wherein R¹, Q, and R², are as defined above, and R³ is alkoxy.

The conversion is accomplished using standard conditions, such as, using either a strong base, e.g NaOH or KOH, or analogous organic bases such as potassium tertiary-butoxide, followed by acidification. (see a similar process in indole chemistry in the A. Galun, et al, reference cited above).

Additionally, the general preparation of a compound of Formula I wherein R⁴ is A, R³ is amino or substituted amino and R¹, Q, and R² are as defined above may also be accomplished as shown in Scheme VII. That is, a mixture of a compound of Formula XX wherein R¹, Q, and R² are as defined above and an alkylaldehyde of from one to four carbons, inclusive in a solvent such as tetrahydrofuran or acetonitrile, is treated with sodium cyanoborohydride. The resulting compound of Formula XXI wherein R⁷ and R⁸ are

independently hydrogen or alkyl of from one to four carbons, inclusive, and R¹ and Q are as defined above is then reacted with R² Cl or R² Br wherein R² is as defined above to obtain the compound of Formula IX. Such a compound of Formula IX, wherein R¹, Q, R² and R⁷ and R⁸ are as defined above may be directly coupled with the compound of Formula II in the presence of lithium diisopropylamine or treated as shown in Schemes VI and further, optionally treated as for Schemes I, II or III as described above.

A compound of Formula XX wherein R¹ is 5-methoxy and Q is hydrogen is known and is prepared by the procedure described in S. V. Simakov, et al, *Khim-Farm. Zh.*, 17, p. 1183 (1983). Other definitions for R¹ and Q in the compound of Formula XX may be prepared by analogous procedures.

The preparation of XXI is generally conducted by the procedures known as reductive amination and the further reaction to convert the compound of Formula XXI to the compound of Formula IX₁, is analogous to the reaction having conditions known as an Ullmann reaction.

Also, the compound of Formula I wherein R⁴ is A, and R³ is alkylthio or alkylsulphonyl may be prepared by the processes shown in Scheme VIII. The compounds of Formula XXX wherein R¹ and Q are as defined above are prepared by known methods, methods analogous to known methods or are commercially available and are reacted with R² Br or R²Cl wherein R² is as defined above using conditions analogous to those described as an Ullmann reaction and shown as step 2 of Scheme VIII. Then the carboxylic acid group is protected, for example, by reaction with CH₃I to form an ester of Formula XXXII wherein R¹, Q, and R² are as defined above and then treated with thionyl chloride in a reaction similar to that described by J. Szmuszkowicz, *J. Org. Chem.*, 29, p 178 (1964) to obtain the sulphonyl chloride of Formula XXXIII wherein R¹, Q, and R² are as defined above.

The compound of Formula XXXIII reacts with a Grignard reagent or an alkyl cuprate reagent to yield alkylsulphonyl or phenyl- or substituted phenylsulphonylindoles of the Formula XXXIV wherein R³ is alkyl of from one to four carbons, inclusive, phenyl or substituted phenyl. The sulphonyl indoles of Formula XXXIV may then be reduced with trifluoroacetic anhydride and sodium iodide to provide the compound of Formula IX, or further reacted to give the compound of Formula IX₃. Again the Formula IX may be coupled with 5-aminotetrazol by various procedures discussed above to give a compound of Formula I wherein R³ is SR⁹ wherein R⁹ is as defined above and R¹, Q, and R² are also as defined above. A compound of Formula I wherein R³ is SR⁹ may of course, be further treated with standard oxidizing reagents such as potassium permanganate or metachloroperbenzoic acid, using conditions analogous to those known for similar reactions to obtain a compound of Formula I wherein R³ is as defined above. The preparation of compounds of Formula I wherein R³ is a sulphur containing group as described hereinabove is shown in Scheme VIII.

Particularly, the processes described above include compounds wherein R¹ is 5-methoxy, Q is hydrogen, and R² is phenyl or benzyl beginning with either a commercially available compound or a compound described by Y. Murakami, et al. in *Synthesis* p 738 (1984).

The 3-alkoxy carboxylic acids of Formula III may be purified by conventional methods or employed without separation in the step shown in Scheme I.

This step is accomplished by methods known in the art, for example, by coupling the 3-alkoxy carboxylic acids of Formula III with 5-aminotetrazole of Formula II, in the presence of coupling agents. Such agents include 1,1'-carbonyldiimidazole and dicyclohexylcarbodiimide. See Scheme II. Appropriate solvents for the step shown in Scheme II may be, for example, N,N-dimethylformamide (DMF), acetonitrile, tetrahydrofuran, chloroform, or dichloromethane. Recrystallization of compounds I, may be accomplished in various solvents, such as N,N-dimethylformamide (DMF) either alone or in combination with H₂O, acetonitrile in combination with water or with DMF and water, acetone, ethyl acetate, methanol alone or in combination with water, 2-methoxyethanol in combination with water, 2-propanol either in combination with water or in combination with DMF and water.

The starting materials required for the processes described in this invention are either commercially available or they can be synthesized by methods known in the art of organic chemistry. For example, an acid intermediate having the Formula III wherein R¹, Q, and R² are hydrogen, R³ is methoxy, is described by N. T. Modi, et al, *J. Org. Chem.*, Vol. 35, 2228 (1970), and a methyl ester of the compound having the Formula III, wherein R¹ and Q are hydrogen, R² is methyl, is as described in French Patent Number 1,503,908 (see *Chem. Abst.*, Vol. 70, 37, 651 (1969). Likewise, an ester of the acid having the Formula III, wherein R¹ is methoxy or chloro, Q is hydrogen, R² is phenyl or 4-methoxyphenyl, R³ is hydroxy, can be prepared in a manner analogous to that described by P. Friedlander, et al, *Chem. Ber.*, Vol. 55, 1597 (1922). Also, various esters of acids of indole compounds for use as precursors in a process of the present invention can be made in view of the teachings of P. C. Unangst, et al, *J. Heterocyclic Chem.*, Vol. 21, 709 (1984).

Under certain circumstances it is necessary to protect either the N or O of intermediates in the above noted process with suitable protecting groups which are known. Introduction and removal of such suitable oxygen and nitrogen protecting groups are well known in the art of organic chemistry; see for example, (1) "Protective Groups in Organic Chemistry," J. F. W. McOmie, ed., (New York, 1973), pages 43ff, 95ff; (2) J. F. W. McOmie, *Advances in Organic Chemistry*, Vol. 3, 191-281 (1963); (3) R. A. Borssenas, *Advances in Organic Chemistry*, Vol. 3, 159-190 (1963); and (4) J. F. W. McOmie, *Chem. & Ind.*, 603 (1979).

Examples of suitable oxygen protecting groups are benzyl, t-butyldimethylsilyl and ethoxyethyl. Protection of an N-H containing moiety is necessary for some of the processes described herein for the preparation of compounds of this invention. Suitable nitrogen protecting groups are benzyl, triphenylmethyl, trialkylsilyl, trichloroethylcarbamate, trichloroethoxycarbonyl and vinyloxycarbamate.

Under certain circumstances it is necessary to protect two different oxygens with dissimilar protecting groups such that one can be selectively removed while leaving the other in place. The benzyl and t-butyldimethylsilyl groups are used in this way; either is removable in the presence of the other, benzyl being removed by catalytic hydrogenolysis, and t-butyldimethylsilyl being removed by reaction with, for example, tetra-n-butylammonium fluoride.

In the process described herein for the preparation of compounds of this invention the requirements for protective groups are generally well recognized by one skilled in the art of organic chemistry, and accordingly the use of appropriate protecting groups is necessarily implied by the processes of the charts herein, although not expressly illustrated.

The products of the reactions described herein are isolated by conventional means such as extraction, distillation and chromatography.

The salts of compounds of Formula I described above are prepared by reacting the appropriate base with a stoichiometric equivalent of the acid indole compounds of Formula I to obtain pharmacologically acceptable salts thereof.

The compounds of this invention may also exist in hydrated or solvated forms.

The process of this invention is further elaborated by the representative examples as follows.

Examples 1 to 23, 30 to 33, and 35 to 38 demonstrate the preparation of intermediates. The remaining Examples demonstrate the use of those intermediates in the preparation of compounds according to the present invention.

EXAMPLE 1

3-Methoxy-1-(phenylmethyl)-1H-indole-2-carboxylic acid

A mixture of 4.6 g (0.096 mole) of 50% sodium hydride/mineral oil in 100 ml of N,N-dimethylformamide under a nitrogen atmosphere was cooled in an ice bath. To the stirred mixture was added over 45 minutes, a solution of 19.5 g (0.089 mole) of 3-methoxy-1H-indole-2-carboxylic acid ethyl ester [A. Galun, A. Markus, and A. Kampf, *J. Heterocyclic Chem.*, 16, 221 (1979)] in 50 ml of N,N-dimethylformamide. The mixture was stirred for an additional 30 minutes, and a solution of 11.6 ml (16.7 g; 0.098 mole) of benzyl bromide in 10 ml of N,N-dimethylformamide was added over 15 minutes. The ice bath was removed, the mixture was stirred for an additional 16 hours, and then added to 800 g of ice water. The crude ester intermediate was removed by extracting with dichloromethane (4 x 250 ml). The combined organic layers were back-washed with brine (3 x 500 ml), dried (anhydrous sodium sulphate), and evaporated to yield a crude residue of 3-methoxy-1(phenylmethyl)-1H-indole-2-carboxylic acid ethyl ester, plus a small amount of N,N-dimethylformamide.

The total crude residue described above was dissolved in 180 ml of methanol and treated with a solution of 14.2 g (0.25 mole) of potassium hydroxide in 180 ml of water. The mixture was stirred at reflux for three hours, cooled, condensed to approximately one-third its original volume (rotary evaporator), and partitioned between 750 ml of water and 300 ml of dichloromethane. The aqueous layer was separated, washed with fresh dichloromethane (2 x 300 ml), filtered, and cooled in ice. Acidification with 4.0 N hydrochloric acid yielded the crude carboxylic acid product. The product was filtered and washed with water to yield 17.1 g (68% yield) of final product. A sample recrystallized from ethyl acetate/hexane was analytically pure, mp 115-117°C.

EXAMPLE 2

1-Hexyl-3-methoxy-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 1 from 27.0 g (0.12 mole) of 3-methoxy-1H-indole-2-carboxylic acid ethyl ester [A. Galun, A. Markus, and A. Kampf, *J. Heterocyclic Chem.*, **16**, 221 (1979)] alkylated with 22.1 g (0.13 mole) of 1-bromohexane.

Saponification of 20.7 g (0.068 mole) of the crude intermediate 1-hexyl-3-methoxy-1H-indole-2-carboxylic acid ethyl ester as described in Example 1 yielded 14.1 g (75% yield) of the crude carboxylic acid product. A sample recrystallised several times from hexane was analytically pure, mp 65-67° C.

EXAMPLE 3

3,5-Dimethoxy-1-phenyl-1H-indole-2-carboxylic acid

A mixture of 10.8 g (0.036 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, *J. Heterocyclic Chem.*, **21**, 709 (1984)] and 5.5 g (0.040 mole) of anhydrous potassium carbonate in 100 ml of acetone was treated with 3.7 ml (4.9 g; 0.039 mole) of dimethyl sulphate. The mixture was stirred and heated at reflux for 16 hours, cooled, and filtered. The filter cake was washed several times with fresh acetone, and the combined filtrates were evaporated (vacuum) to yield a crude residue of 3,5-dimethoxy-1-phenyl-1H-indole-2-carboxylic acid ethyl ester.

The total crude residue described above was saponified with 6.3 g (0.11 mole) of potassium hydroxide by the procedure described in Example 1. There was obtained 9.8 g (91% yield) of crude carboxylic acid. Recrystallization from aqueous acetone yielded the carboxylic acid product in analytical purity, mp 150° C-dec.

EXAMPLE 4

3-Methoxy-1-phenyl-1H-indole-2-carboxylic acid

A suspension of 3.9 g (0.081 mole) of 50% sodium hydride/mineral oil in 85 ml of N,N-dimethylformamide under a nitrogen atmosphere was cooled in ice and treated portionwise over 90 minutes with 17.1 g (0.064 mole) of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. Friedlander and K. Kunz, *Chem. Ber.*, **55**, 1597 (1922)]. The mixture was stirred in ice an additional one hour, 7.9 ml (10.5 g; 0.083 mole) of dimethyl sulphate was added dropwise over 15 minutes, the ice bath was removed, and stirring was continued for a total of 65 hours. The reaction mixture was added to 600 g of ice/water, acidified with 4.0 N hydrochloric acid, and extracted with dichloromethane (4 x 250 ml). The combined organic layers were washed with water (3 x 500 ml), dried (anhydrous sodium sulphate), and evaporated to yield a crude residue of 3-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester, plus a small amount of N,N-dimethylformamide.

The total crude residue described above was saponified with 11.4 g (0.20 mole) of potassium hydroxide by the procedure described in Example 1. There was obtained 14.4 g (84% yield) of crude carboxylic acid product. A sample recrystallized from ethyl acetate/hexane was analytically pure, mp 115° C-dec.

EXAMPLE 5

1-Phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid
methyl ester

A mixture of 1.2 g (0.025 mole) of 50% sodium hydride/mineral oil suspension in 20 ml of hexamethylphosphoramide under a nitrogen atmosphere was cooled in ice and treated over 15 minutes with a solution of 5.3 g (0.020 mole) of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. Friedlander and K. Kurz, Chem. Ber., 55; 1597 (1922)] in 25 ml of hexamethylphosphoramide. The mixture was stirred in ice an additional one hour, 2.6 ml (2.9 g, 0.023 mole) of benzyl chloride was added in one portion, the ice bath was removed and stirring was continued for a total of 18 hours. The reaction mixture was added to 200 g of ice/water, stirred for one hour, and the precipitated product was filtered and washed with water. Recrystallization from aqueous methanol yielded 3.8 g (54% yield) of the ester product. An additional recrystallization as above yielded analytically pure ester, mp 117-119 °C.

EXAMPLE 6

1-Phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid

A mixture of 11.9 g (0.033 mole) of the ester described in Example 5 in 200 ml of dimethyl sulphoxide under a nitrogen atmosphere was treated with 7.4 g (0.066 mole) of potassium tert-butoxide. The mixture was stirred and heated to 65 °C for two hours, cooled, and added to 2.5 kg ice/water. The aqueous mixture was filtered, and the filtrate was cooled in ice and acidified with 6.0 N hydrochloric acid to precipitate the crude carboxylic acid product. The product was filtered and washed with water to yield 9.7 g (89% yield) of final product. A sample recrystallized from ethyl acetate/hexane was analytically pure, mp 140-142 °C.

EXAMPLE 7

5-Methoxy-1-phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid

A mixture of 155 g (0.52 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1984)], 83.0 g (0.60 mole) of anhydrous potassium carbonate, and 68 ml (97.8 g; 0.57 mole) of benzyl bromide in 2250 ml of acetone was stirred at reflux for 20 hours. The mixture was cooled, filtered, and the filter cake was washed several times with fresh acetone. The combined filtrates were evaporated (vacuum) to yield a crude residue of 5-methoxy-1-phenyl-3-(phenylmethoxy)-1H-indole-2-carboxylic acid methyl ester.

The total crude residue described above was dissolved in 1.0 l of methanol. The solution was treated with a solution of 83 g (1.48 mole) of potassium hydroxide in 1.0 l of water, and the new mixture was stirred at reflux for three hours. The reaction mixture was cooled, filtered, and the filtrate was added to 7.0 kg of ice/water. The aqueous solution was cooled in ice and acidified with glacial acetic acid to precipitate the crude carboxylic acid product. The product was filtered and washed with water to yield 174 g (89% yield) of final product. A sample recrystallized from aqueous acetone was analytically pure, mp 123 °C-dec.

EXAMPLE 8

5 5-Methoxy-3-(1-methylethoxy)-1-phenyl-1H-indole-2-
carboxylic acid

10 A stirred mixture of 24.8 g (0.22 mole) of potassium tert-butoxide in 100 ml of dimethyl sulphoxide (under a nitrogen atmosphere) was placed in a cold water bath. A solution of 44.6 g (0.15 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1984)] in 100 ml of dimethyl sulfoxide was added over 30 minutes. The new mixture was stirred for an additional 45 minutes, and 25.0 ml (32.8 g, 0.27 mole) of 2-bromopropane was added in one portion. The cooling bath was removed, and the mixture was stirred at room temperature
 15 for 45 hours, then added to 2.5 kg ice water. The crude ester intermediate was removed by extracting with dichloromethane (4 x 800 ml). The combined organic layers were washed with water (1 x 2.0 l), 5% aqueous sodium bicarbonate (2 x 2.0 l), and water again (1 x 2.0 l), before being dried with anhydrous sodium sulphate. Evaporation (vacuum) yielded a crude residue of 5-methoxy-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester.

20 The total crude residue described above was dissolved in 300 ml of methanol and the solution was treated with a solution of 22.5 g (0.40 mole) of potassium hydroxide in 300 ml of water. The mixture was stirred at reflux for three hours, cooled, and condensed on a rotary evaporator until a precipitate began to form. After standing for several hours, the precipitated carboxylic acid potassium salt was filtered and washed with cold acetone. The solid was dissolved in 850 ml of water plus 140 ml of acetone by warming
 25 slightly. The new solution was cooled in ice and treated with 10 ml of glacial acetic acid to precipitate the crude product. The solid was filtered and washed with water to yield 33.4 g (68% yield) of the carboxylic acid product. A sample recrystallized from aqueous methanol was analytically pure, mp 110° C-dec.

EXAMPLE 9

30 3-Ethoxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid

35 Prepared by the procedure described in Example 8 from 30.0 g (0.10 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester alkylated with 67.5 ml (79.4 g; 0.51 mole) of diethyl sulphate.

40 The crude 3-ethoxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 1 to yield 27.5 g (88% yield) of the crude carboxylic acid product. A sample recrystallized several times from aqueous methanol was analytically pure, mp 130° C-dec.

EXAMPLE 10

45 3-Hydroxy-1-(4-methoxyphenyl)-1H-indole-2-carboxylic
acid methyl ester

50 Prepared in a manner analogous to the multi-step procedure described [P. Friedlander and K. Kunz, Chem. Ber., 55, 1597 (1922)] for the preparation of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester, with 2-(4-methoxyphenylamino)benzoic acid substituted for 2-(phenylamino)benzoic acid in the first step of the synthetic sequence. The final indole product was recrystallized from 2-propanol to yield
 55 analytically pure product, mp 153-155° C.

EXAMPLE 11

5 1-(4-Methoxyphenyl)-3-(1-methylethoxy)-1H-indole-2-
carboxylic acid methyl ester

10 Prepared by the procedure described in Example 8 from 5.0 g (0.017 mole) of 3-hydroxy-1-(4-methoxyphenyl)-1H-indole-2-carboxylic acid methyl ester alkylated with 3.6 ml (4.7 g; 0.038 mole) of 2-bromopropane. After addition of the total reaction mixture to water, the precipitate was filtered and washed with water to yield 5.6 g (95% yield) of crude ester product. A sample recrystallized from methanol was analytically pure, mp 129-131°C.

15 EXAMPLE 12

20 1-(4-Methoxyphenyl)-3-(1-methylethoxy)-1H-indole-2-
carboxylic acid

25 Prepared by the saponification procedure described in Example 7 from 5.0 g (0.015 mole) of 1-(4-methoxyphenyl)-3-(1-methylethoxy)-1H-indole-2-carboxylic acid methyl ester and 12.0 g (0.20 mole) of potassium hydroxide. The crude product was recrystallized from ether/hexane to yield 3.8 g (78% yield) of analytically pure carboxylic acid product, mp 129°C-dec.

EXAMPLE 13

30 5-Chloro-3-hydroxy-1-phenyl-1H-indole-2-carboxylic
acid methyl ester

35 Prepared in a manner analogous to the multi-step procedure described [P. Friedlander and K. Kunz, Chem. Ber., 55, 1597 (1922)] for the preparation of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester, with 5-chloro-2-(phenylamino)benzoic acid substituted for 2-(phenylamino)benzoic acid in the first step of the synthetic sequence. The final indole product was recrystallized from aqueous 2-methoxyethanol to yield analytically pure product, mp 170-173°C.

EXAMPLE 14

45 5-Chloro-3-(1-methylethoxy)-1-phenyl-1H-indole-2-
carboxylic acid

50 Prepared by the procedure described in Example 8 from 13.9 g (0.046 mole) of 5-chloro-3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester alkylated with 7.7 ml (10.1 g; 0.082 mole) of 2-bromopropane.

55 The crude 5-chloro-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate (14.8 g; 0.04 mole) was saponified with 6.4 g (0.11 mole) of potassium hydroxide as described in Example 1 to yield 10.2 g (72% yield) of the crude carboxylic acid product, mp 120°C-dec. This material was used for further synthesis without additional purification.

EXAMPLE 15

3-Methoxy-1-nonyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 1 from 20.0 g (0.091 mole) of 3-methoxy-1H-indole-2-carboxylic acid ethyl ester [A. Galun, A. Markus, and A. Kampf, *J. Heterocyclic Chem.*, **16**, 221 (1979)], alkylated with 19 ml (20.6 g; 0.099 mole) of n-nonyl bromide.

The crude 3-methoxy-1-nonyl-1H-indole-2-carboxylic acid ethyl ester intermediate was saponified as described in Example 1 to yield 18.0 g (62% yield) of the crude carboxylic acid product. This material was used for further synthesis without additional purification.

EXAMPLE 16

3-(1-Methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 8 from 9.5 g (0.036 mole) of 3-hydroxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. Friedlander and K. Kunz; *Chem. Ber.*, **55**, 1597 (1922)], alkylated with 5.9 ml (7.7 g; 0.063 mole) of 2-bromopropane.

The crude 3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 1 to yield 8.3 g (79% yield) of the crude carboxylic acid product, mp 100°-dec. This material was used for further synthesis without additional purification.

EXAMPLE 17

5-Methoxy-3-(n-nonyloxy)-1-phenyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 7 from 20.0 g (0.067 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, *J. Heterocyclic Chem.*, **21**, 709 (1984)], alkylated with 14 ml (15.2 g; 0.073 mole) of n-nonyl bromide.

A 1.0 g (0.0024 mole) sample of the crude 5-methoxy-3-(n-nonyloxy)-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 6 (except that the saponification was carried out at 25°C for 18 hours) to yield 0.35 g (36% yield) of the crude carboxylic acid product, mp 81-84°C. This material was used for further synthesis without additional purification.

EXAMPLE 18

3-(n-Dodecyloxy)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid

Prepared by the procedure described in Example 8 from 10.0 g (0.034 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester [P. C. Unangst and M. E. Carethers, *J. Heterocyclic Chem.*, **21**, 709 (1984)], alkylated with 12.6 g (0.037 mole) of n-dodecyl p-toluene-sulfonate [C. S. Marvel and C. C. Sekera, *Organic Syntheses Coll. Vol. 3*, p. 366].

A 1.0 g (0.0022 mole) sample of the crude 3-(n-dodecyloxy)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid methyl ester intermediate was saponified as described in Example 6 (except that the reaction was

carried out at 25° C for 21 hours) to yield 0.38 g (39% yield) of the crude carboxylic acid product, mp 85-87° C. This material was used for further synthesis without additional purification.

EXAMPLE 19

2-[(Carboxymethyl)methylamino]-5-methoxybenzoic acid

A mixture of 244 g (0.91 mole) of the potassium salt of 2-bromo-5-methoxybenzoic acid (prepared by treating a solution of the parent carboxylic acid in 2-propanol with excess methanolic potassium hydroxide), 196 g (1.54 mole) of the potassium salt of N-methylglycine (prepared as above), 13 g (0.82 mole) of anhydrous potassium carbonate and 0.66 g (0.01 mole) of copper powder in 220 ml of water was stirred at reflux for five hours. The mixture was cooled, added to 4.0 kg of ice/water, and acidified with concentrated hydrochloric acid to precipitate the crude product. The solid was filtered and washed with water to yield 186 g (86% yield) of the carboxylic acid product. A sample recrystallized from aqueous 2-methoxyethanol was analytically pure, mp 196° C-dec.

EXAMPLE 20

2-[(Carboxymethyl)methylamino]-5-methoxybenzoic acid dimethyl ester

A mixture of 186 g (0.78 mole) of 2-[(carboxymethyl)methylamino]-5-methoxybenzoic acid in 1.0 l of N,N-dimethylformamide was stirred and treated with a 25% aqueous solution of sodium hydroxide (62.2 g; 1.56 mole). The mixture was stirred for an additional 20 minutes, and 139 ml (316 g; 2.22 mole) of iodomethane was added in one portion. After stirring for 16 hours, the mixture was added to 4.0 kg of ice/water, and the ester product was removed by extracting with dichloromethane (4 x 1.5 l). The combined organic layers were washed with water (1 x 2.0 l), saturated aqueous sodium bicarbonate (3 x 2.0 l), and water again, dried (anhydrous sodium sulphate), and evaporated. The crude diester residue (containing some residual N,N-dimethylformamide) was cyclized to the corresponding indole without additional purification.

EXAMPLE 21

3-Hydroxy-5-methoxy-1-methyl-1H-indole-2-carboxylic acid methyl ester

The total crude diester residue described in Example 20 was dissolved in 1.0 l of methanol under a nitrogen atmosphere. To the stirred mixture was added 54.6 g (1.01 mole) of sodium methoxide in one portion. The mixture was stirred at reflux for three hours, cooled, added to 4.0 kg of ice/water, and acidified with glacial acetic acid to precipitate the product. The solid was filtered and washed with water to yield 71.7 g (39% yield) of the indole product. A sample recrystallized from aqueous methanol was analytically pure, containing 0.25 mole of water of hydration, mp 103-105° C.

EXAMPLE 22

5-Methoxy-1-methyl-3-(1-methylethoxy)-1H-indole-2-carboxylic acid methyl ester

Prepared by the procedure described in Example 8 from 69.6 g (0.30 mole) of 3-hydroxy-5-methoxy-1-methyl-1H-indole-2-carboxylic acid methyl ester alkylated with 27.8 ml (36.3 g; 0.30 mole) of 2-bromopropane. After addition of the total reaction mixture to water, the precipitate was filtered and washed with water to yield 45 g (55% yield) of crude ester product. A sample recrystallized from aqueous ethanol was analytically pure, mp 87-89° C.

EXAMPLE 23

5-Methoxy-1-methyl-3-(1-methylethoxy)-1H-indole-2-
carboxylic acid

Prepared by the saponification procedure described in Example 7 from 41.2 g (0.15 mole) of 5-methoxy-1-methyl-3-(1-methylethoxy)-1H-indole-2-carboxylic acid methyl ester and 16.7 g (0.30 mole) of potassium hydroxide. The crude acid product was 18.3 g (47% yield). A sample recrystallized from aqueous 2-methoxyethanol was analytically pure, mp 110-112° C.

EXAMPLE 24 (PROCEDURE A)

3-Methoxy-1-(phenylmethyl)-N-1H-tetrazol-5-yl-1H-
indole-2-carboxamide

A mixture of 3.0 g (0.011 mole) of 3-methoxy-1-(phenylmethyl)-1H-indole-2-carboxylic acid and 3.7 g (0.023 mole) of 1,1'-carbonyldiimidazole in 15 ml of N,N-dimethylformamide was stirred and heated on the steam bath under a nitrogen atmosphere for 20 minutes. The mixture was cooled, 1.3 g (0.013 mole) of 5-aminotetrazole monohydrate was added, and heating was continued for an additional 20 minutes. The cooked reaction mixture was added to 150 g of ice/water. Acidification with 4.0 N hydrochloric acid yielded the carbamoyltetrazole product. The crude product was filtered, washed with water, and recrystallized from 2-methoxyethanol/water to yield analytically pure product. There was obtained 2.3 g (63% yield) of product, mp 230° C-dec.

EXAMPLE 25 (PROCEDURE B)

5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-
5-yl-1H-indole-2-carboxamide

A mixture of 20.0 g (0.062 mole) of 5-methoxy-3-(1-methylethoxy)-1-phenyl-1H-indole-2-carboxylic acid and 11.3 g (0.070 mole) of 1,1'-carbonyldiimidazole in 375 ml of acetonitrile was stirred at reflux (under a nitrogen atmosphere) for 90 minutes. The mixture was cooled, and 6.2 g (0.073 mole) of anhydrous 5-aminotetrazole was added, followed by 20.6 ml (15 g; 0.15 mole) of triethylamine. After stirring at reflux for an additional 16 hours, the mixture was cooled, added to 1.5 kg of ice/water and acidified with glacial acetic acid. The precipitated product was filtered and washed with water. Recrystallization from aqueous acetonitrile yielded 19.0 g (79% yield) of analytically pure carbamoyltetrazole product, mp 227° C-dec.

Additionally the following compounds of Formula I may be prepared by methods analogous to Procedures A or B above:

- 3-Methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 235° C-dec.
- 3-Methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 240° C-dec.
- 1-Hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 210° C-dec.
- 3-Methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 199-200° C.
- 3-Methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 215° C-dec.
- 1-Phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 208° C-dec.
- 3-(1-Methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 203-205° C.
- 1-(4-Methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 166° C-dec.
- 5-Chloro-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 228° C-dec.
- 5-Methoxy-1-methyl-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 222-225° C.
- 3,5-Dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 220° C-dec.

3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 226° C-dec.
 5-Methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 212° C-dec.
 5-Methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 203-204° C.
 3-(n-Dodecyloxy)5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 185-186° C.

EXAMPLE 26

5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-
5-yl-1H-indole-2-carboxamide L-arginate salt

A suspension of 2.76 g (0.007 mole) of 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide in 40 ml of methanol was warmed on a steam bath and treated with a solution of 1.22 g (0.007 mole) of L-arginine dissolved in a minimum of hot water. The mixture was digested until nearly one phase and filtered hot. Cooling to room temperature resulted in precipitation of the arginine salt product. The solid was filtered and washed several times with cold acetone to yield 2.77 g (70% yield) of analytically pure arginine salt, containing 0.50 mole of water of hydration, mp 218° C-dec.

EXAMPLE 27

5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-
5-yl-1H-indole-2-carboxamide sodium salt

A suspension of 7.85 g (0.020 mole) of 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide in 175 ml of methanol was warmed on the steam bath and treated with 10.0 ml of 2.0 N aqueous sodium hydroxide solution. The mixture was digested for a few minutes, filtered hot, cooled, and evaporated. The residue was redissolved and reevaporated several times in 50% acetone/methanol. There was obtained 7.5 g (90% yield) of the amorphous sodium salt product, analytically pure containing 1.0 equivalent of water of hydration, mp 205° C-dec.

EXAMPLE 28

3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-
indole-2-carboxamide L-arginate salt

Prepared by the procedure described in Example 26 from 2.8 g (0.0074 mole) of 3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide and 1.3 g (0.0075 mole) of L-arginine, except that the solvent was ethanol rather than methanol. There was obtained 2.6 g (63% yield) of the arginine salt product, analytically pure containing 1.0 equivalent of water of hydration, mp 165° C-dec.

EXAMPLE 29

3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-
indole-2-carboxamide sodium salt

Prepared by the procedure described in Example 27 from 7.57 g (0.020 mole) of 3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, and 10.0 ml of 2.0 N aqueous sodium hydroxide solu-

tion. There was obtained 7.27 g (91% yield) of the amorphous sodium salt product, analytically pure containing 0.50 equivalent of water of hydration, mp 195 °C-dec.

EXAMPLE 30

2-[(Cyanomethyl)phenylamino]-5-methoxybenzoic acid methyl ester

A mixture of 7.1 g (0.025-mole) of 2-[(cyanomethyl)phenylamino]-5-methoxybenzoic acid [P. C. Unangst and M. E. Carethers, J. Heterocyclic Chem., 21, 709 (1974)], 4.0 g (0.029 mole) of anhydrous potassium carbonate, and 3.0 ml (4.0 g; 0.032 mole) of dimethyl sulphate in 200 ml of acetonitrile was stirred at reflux for 24 hours. The mixture was cooled and filtered, and the filter cake was washed several times with fresh acetonitrile. The combined filtrates were evaporated to an oil, which crystallized upon standing at room temperature. Recrystallization from aqueous methanol yielded 5.1 g (68% yield) of the ester product. A sample recrystallized again as above was analytically pure, mp 107-109 °C.

EXAMPLE 31

3-Hydroxy-5-methoxy-1-phenyl-1H-indole-2-carbonitrile

A mixture of 8.4 g (0.075 mole) of potassium tert-butoxide in 200 ml of tetrahydrofuran (under a nitrogen atmosphere) was stirred and cooled in an ice bath. A solution of 13.7 g (0.046 mole) of 2-[(cyanomethyl)phenylamino]-5-methoxybenzoic acid methyl ester in 150 ml of tetrahydrofuran was added over two hours, the ice bath was removed, and the new mixture was stirred for an additional 42 hours. The total reaction mixture was added to 1.1 kg of ice/water and acidified with 12.0 ml of glacial acetic acid to precipitate the crude product. The solid was filtered, washed with water, and recrystallized from aqueous methanol to yield 10.3 g (84% yield) of the nitrile product. A sample recrystallized again as above was analytically pure, mp 182 °C-dec.

EXAMPLE 32

3-Ethoxy-5-methoxy-1-phenyl-1H-indole-2-carbonitrile

Prepared by the procedure described in Example 8 from 2.2 g (0.0083 mole) of 3-hydroxy-5-methoxy-1-phenyl-1H-indole-2-carbonitrile alkylated with 3.3 ml (3.9 g; 0.025 mole) of diethyl sulphate. The crude product was recrystallized from aqueous propanol to yield 1.6 g (67% yield) of the alkylated nitrile product. An additional recrystallization as above yielded an analytically pure sample, mp 97-99 °C.

EXAMPLE 33

3-(Diethylamino)-5-methoxy-1H-indole -2-carboxylic acid, ethyl ester

A stirred solution of 12.0 g (0.051 mole) of 3-amino-5-methoxy-1H-indole-2-carboxylic acid, ethyl ester (S. V. Simakov, et al, Khim-Farm Zh., 17, 1183 (1983) and 11.5 g (0.26 mole) of acetaldehyde in 250 ml of acetonitrile (under a nitrogen atmosphere) was cautiously treated with 14.0 g (0.22 mole) of sodium cyanoborohydride. After stirring for 15 minutes, 4.0 ml (4.2g; 0.07 mole) of acetic acid was added in portions over two hours. The reaction mixture was poured over a mixture of ice and 400 ml of 1.0 N sodium hydroxide solution, and the new mixture was extracted with ether. The combined ether layers were washed several times with brine, dried (anhydrous magnesium sulfate), and evaporated to an orange oil. Flash chromatographic purification (silica gel, methylene chloride/ethyl acetate/hexane (1:6:3) elution) of the residual oil yielded 11.5 g (76% yield) of the analytically pure ester product, mp 85-89 °C.

EXAMPLE 34

3-(Diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

5 A mixture of 3.0 g (0.010 mole) of 3-(diethylamino)-5-methoxy-1H-indole-2-carboxylic acid, ethyl ester, 5.0 g (0.036 mole) of potassium carbonate, 0.50 g (0.009 mole) of potassium hydroxide, 0.30 g (0.001 mole) of copper(I)bromide, and 30.0 ml (44.7 g; 0.28 mole) of bromobenzene under an argon atmosphere was stirred and heated at reflux for three hours. The reaction mixture was filtered while hot through a bed of Celite® filter-aid. The filter cake was washed twice with warm toluene, and the combined filtrates were
 10 evaporated. The residue was dissolved in a small amount of dichloromethane and purified by flash chromatography (silica gel, 15% ethyl acetate in hexane elution) to yield 2.4 g (66% yield) of intermediate, 3-(diethylamino)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, ethyl ester, as an oil.

A solution of 2.0 ml (1.44 g; 0.014 mole) of diisopropylamine in 20 ml of tetrahydrofuran under a nitrogen atmosphere was cooled to -10 °C and treated with 5.4 ml (0.014 mole) of 2.6 M n-butyllithium in
 15 hexane. After stirring for five minutes, a solution of 0.43 g (0.0051 mole) of anhydrous 5-aminotetrazole in 20 ml of 1,3-dimethyl-2-imidazolidinone was added dropwise. The reaction mixture was stirred for two hours at -10 °C, and then a solution of 1.7g (0.0046 mole) of the previously described 3-(diethylamino)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, ethyl ester in 20 ml of tetrahydrofuran was added dropwise. The new mixture was stirred for three hours at -10 °C, then quenched by the addition of aqueous saturated
 20 ammonium chloride solution. The total reaction mixture was added to 100 ml of ice water and extracted twice with ether (organic layers discarded). The aqueous phase was cooled in ice and acidified to pH 4 with dilute hydrochloric acid to precipitate 0.25 g (13% yield) of the carbamoyltetrazole product, mp 105-112 °C.

EXAMPLE 35

5-Methoxy-1-phenyl-1H-indole-2-carboxylic acid

A mixture of 60.0 g (0.32 mole) of 5-methoxy-1H-indole-2-carboxylic acid, 35.0 ml (52.2 g; 0.32 mole) of bromobenzene, 36.0 g (0.64 mole) of potassium hydroxide, and 10.0 g (0.13 mole) of copper (II) oxide in
 30 750 ml of N,N-dimethylformamide was stirred and heated at reflux under a nitrogen atmosphere for six hours. The cooled reaction mixture was added to 1.5 kg of ice/water and filtered through a bed of Celite® filter-aid. Acidification of the filtrate with dilute hydrochloric acid precipitated the product. The solid was filtered and washed with water to yield 83.0g (95% yield) of crude acid product. A sample recrystallized from ether/hexane was analytically pure, mp 197-204 °C.

EXAMPLE 36

5-Methoxy-1-phenyl-1H-indole-2-carboxylic acid, methyl ester

A solution of 30.0g (0.11 mole) of 5-methoxy-1-phenyl-1H-indole-2-carboxylic acid in 300 ml of N,N-dimethylformamide was treated with 9.6 g (0.12 mole) of 50% aqueous sodium hydroxide solution. The new
 40 mixture was stirred for 15 minutes, 8.0 ml (18.4g; 0.13 mole) of iodomethane was added, and stirring was continued at room temperature for four hours. The reaction mixture was added to 1.0 l of cold water and extracted with dichloromethane. The combined organic layers were washed twice with water, dried (anhydrous magnesium sulphate) and evaporated. Recrystallization of the residue from petroleum ether
 45 yielded 25 g (82% yield) of the analytically pure ester product, mp 67-68 °C.

EXAMPLE 37

5-Methoxy-3-(methylsulphinyl)-1-phenyl-1H-indole-2-carboxylic acid, methyl ester

A mixture of 4.0 g (0.014 mole) of 5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, methyl ester in 7.0 ml (11.4g; 0.096 mole) of thionyl chloride (under a nitrogen atmosphere) was stirred at ambient temperature for ten minutes. After the addition of 50 ml of 20% hexane in ether solution, the new mixture was cooled in
 55 ice for 30 minutes to precipitate the crude intermediate sulphinyl chloride. The solid was filtered and washed with hexane to yield 3.0 g (63% crude yield) of 3-(chlorosulphinyl)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, methyl ester.

The total crude intermediate described above (3.0g; 0.0087 mole) was dissolved (under a nitrogen atmosphere) in 100 ml of tetrahydrofuran and cooled to -70 °C. After dropwise addition of 15.0 ml (0.015

mole) of methyl magnesium bromide (1.0 M in ether), the new mixture was stirred at -70 °C for 15 minutes, then quenched by the careful addition of 10.0 ml of 10% aqueous hydrochloric acid. The product was extracted with ether, and the combined organic layers were washed several times with brine and dried (anhydrous magnesium sulphate). Evaporation of the ether solution yielded an oil which was subjected to
 5 flash chromatography (silica gel, 50% ethyl acetate/chloroform elution) to yield 2.7 g (57% yield) of the analytically pure methylsulfinyl indole product, mp 140-144 °C.

By variation of the Grignard reagent employed in the second part of the above procedure, also prepared were:

5-Methoxy-3-[(1-methylethyl)sulphinyl]-1-phenyl-1H-indole-2-carboxylic acid, methyl ester), mp 103-104 °C;
 10 and

5-Methoxy-1-phenyl-3-(phenylsulphinyl)-1H-indole-2-carboxylic acid, methyl ester, mp 146-148 °C.

EXAMPLE 38

15 5-Methoxy-3-(methylthio)-1-phenyl-1H-indole-2-carboxylic acid

A mixture of 8.0 g (0.023 mole) of 5-methoxy-3-(methylsulphinyl)-1-phenyl-1H-indole-2-carboxylic acid, methyl ester and 10.0 g (0.067 mole) of sodium iodide in 200 ml of acetone (under a nitrogen atmosphere) was maintained at 0-5 °C and treated dropwise with 10.0 ml (14.9g; 0.071 mole) of trifluoroacetic anhydride.
 20 The reaction mixture was stirred for ten minutes, then poured into 300 ml of ice/5% sodium bicarbonate solution. The product was extracted with ether, and the combined extracts were washed with 5% aqueous sodium thiosulfate solution, followed by brine. The organic layer was dried (anhydrous magnesium sulfate) and evaporated to yield 7.5 g (100% yield) of crude intermediate 5-methoxy-3-(methylthio)-1-phenyl-1H-indole-2-carboxylic acid, methyl ester as an oil.

25 The total crude intermediate ester described above (7.5g, 0.023 mole) was dissolved in 200 ml of methanol and treated with 55.0 ml (0.11 mole) of 2.0 N aqueous sodium hydroxide solution. The mixture was stirred at 60 ° for 2.5 hours, cooled, and added to 500 g ice/water. Acidification with 10% hydrochloric acid followed by filtration and washing with water yielded 5.0 g (67% yield) of the analytically pure carboxylic acid product, mp 161-163 °C (dec.).

30 Similarly prepared by the above procedures from the appropriate sulphinyl esters were:

5-Methoxy-1-phenyl-3-(phenylthio)-1H-indole-2-carboxylic acid, mp 153-156 °C and

5-Methoxy-3-[(1-methylethyl)thio]-1-phenyl-1H-indole-2-carboxylic acid and

5-Methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-1H-indole-2-carboxylic acid; the latter two compounds were non-crystalline and were converted to the carbamoyltetrazoles without extensive purification.

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EXAMPLE 39

5-Methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

40 A mixture of 1.2 g (0.0038 mole) of 5-methoxy-3-(methylthio)-1-phenyl-1H-indole-2-carboxylic acid and 0.74 g (0.0046 mole) of 1,1'-carbonylbis (1H-imidazole) in 50 ml of acetonitrile was stirred at 50 °C under a nitrogen atmosphere for one hour. The reaction mixture was cooled slightly and treated with a mixture of 0.40 g (0.0047 mole) of anhydrous 5-aminotetrazole and 1.1 ml (0.80 g; 0.0079 mole) of triethylamine in 25 ml of warm acetonitrile. The new mixture was then stirred at 50 ° for 16 hours, cooled, and added to 200 g
 45 of ice/H₂O. Acidification to pH 4 with acetic acid precipitated the crude product, which was filtered and washed with water. Recrystallization from 30% acetonitrile in 2-propanol yielded 0.92 g (64% yield) of analytically pure carbamoyltetrazole product, mp 252-253 °C.

Similarly prepared by the above procedure from the appropriate carboxylic acid were:

5-Methoxy-3-[(1-methylethyl)thio]-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide mp 247-250 °C
 50 (dec.);

5-Methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide mp 254-256 °C (dec.) and

5-Methoxy-1-phenyl-3-(phenylthio)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, mp 243-245 °C (dec.).

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EXAMPLE 40

5-Methoxy-3-(methylsulphonyl)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

5 A solution of 1.2g (0.0032 mole) of 5-methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide in 75 ml of water containing 0.27 g (0.0032 mole) of sodium bicarbonate was treated with a slurry of 2.0 g (0.013 mole) of potassium permanganate in 75 ml of acetone. After stirring at ambient temperature for two hours, the mixture was filtered through a bed of Celite® filter-aid. The filtrate was cooled in ice and acidified to pH 4 with acetic acid to precipitate the crude sulphone product. The solid was
 10 filtered, washed with water, and recrystallized from 2-propanol/acetonitrile/water (10/20/1) to yield 0.38 g (28% yield) of the analytically pure sulphone product, mp 263 °C dec.

EXAMPLE 41

5-Methoxy-3-[(1-methylethyl)sulphonyl]-1-phenyl-1H-indole-2-carboxylic acid

A solution of 3.0 g (0.0081 mole) of 5-methoxy-3-[(1-methylethyl)sulphonyl]-1-phenyl-1H-indole-2-carboxylic acid, methyl ester in 250 ml of acetone was treated with a slurry of 2.6 g (0.016 mole) of potassium permanganate in 50 ml of water. After stirring at ambient temperature for four hours, the excess oxidant was
 20 destroyed by the addition of solid potassium iodide. The reaction mixture was filtered through a bed of Celite® filter-aid, and a volume of water equivalent to that of the filtrate was added. The precipitated solid was filtered and washed with water to yield 1.2 g (40% yield) of intermediate sulfone 5-methoxy-3-[(1-methylethyl)sulphonyl]-1-phenyl-1H-indole-2-carboxylic acid, methyl ester, mp 164-166 °C.

A 1.0 g (0.0026 mole) sample of the above sulphone ester was saponified with sodium hydroxide as described in Example 38 to yield 0.75 g (77% yield) of the corresponding sulphone carboxylic acid, mp 171-173 °C.

EXAMPLE 42

5-Methoxy-3-[(1-methylethyl)sulphonyl]-1-phenylmethyl 1H-indole-2-carboxylic acid, ethyl ester

A suspension of 7.0 g (0.023 mole) of 5-methoxy-1-phenylmethyl-1H-indole-2-carboxylic acid, ethyl ester (Y. Murakami, et al, Synthesis, 738 (1984)) in 75 ml of n-heptane under an argon atmosphere was cooled in ice and treated with 15.0 ml (24.5 g; 0.21 mole) of thionyl chloride. The mixture was stirred for 30
 35 minutes, and the precipitated sulphonyl chloride intermediate was filtered and washed several times with hexane to yield 7.3 g (76% yield) of 3-(chlorosulphonyl)-5-methoxy-1-phenylmethyl-1H-indole-2-carboxylic acid, ethyl ester.

The total crude intermediate described above was treated with isopropylmagnesium bromide in a manner analogous to that described in Example 37. Flash chromatographic purification (silica gel, 10% ethyl acetate in hexane elution) of the initial oil product yielded 4.2 g (46% yield) of the analytically pure (1-methylethyl)sulphonyl indole ester product, mp 97-99 °C.

EXAMPLE 43

3-(Diethylamino)-5-methoxy-1-phenyl-1H-indole-2 carboxylic acid

A mixture of 2.4 g (0.0066 mole) of 3-(diethylamino)-5-methoxy-1-phenyl-1H-indole-2-carboxylic acid, ethyl ester (prepared as described in Example 34), and 1.6 g (0.040 mole) of sodium hydroxide in 50 ml of ethanol plus 15 ml of water was stirred at 65 °C for four hours. The reaction mixture was cooled, added to 250 g ice/brine, and acidified to pH 2 with dilute hydrochloric acid. The product was extracted with ether, and the combined organic layers were washed twice with brine and dried (anhydrous magnesium sulphate). Evaporation of the ether solution left a solid residue, which was triturated with ether/hexane to yield 1.55 g (70% yield) of the crude acid product. A sample recrystallized from ether/hexane was analytically pure, mp
 55 141-143 °C.

SCHEME I

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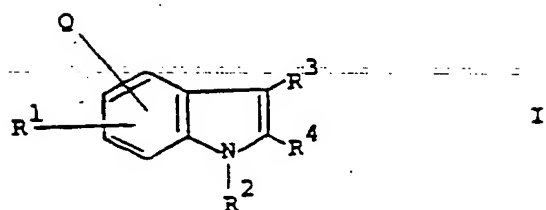
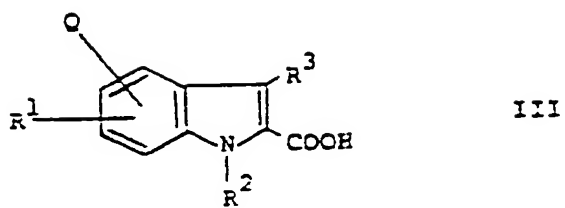
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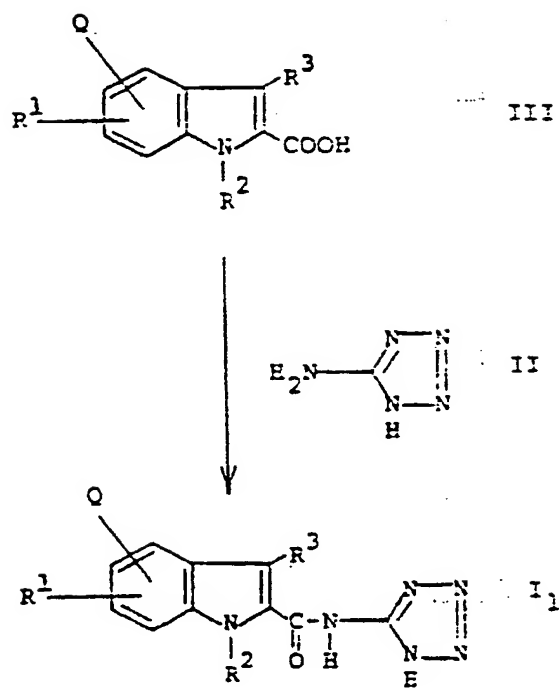
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SCHEME II



SCHEME III

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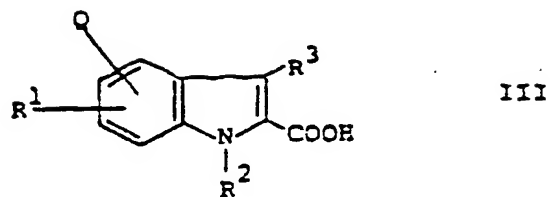
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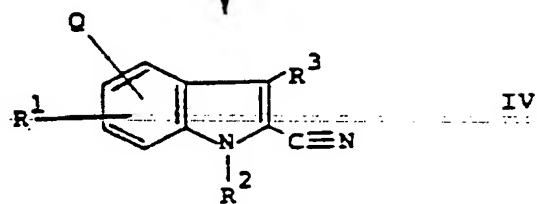
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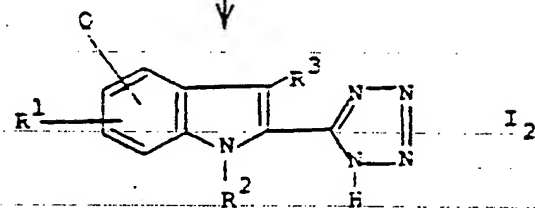


Step I

- 1) H_2NR
- 2) $-H_2O$



Step II



SCHEME IV

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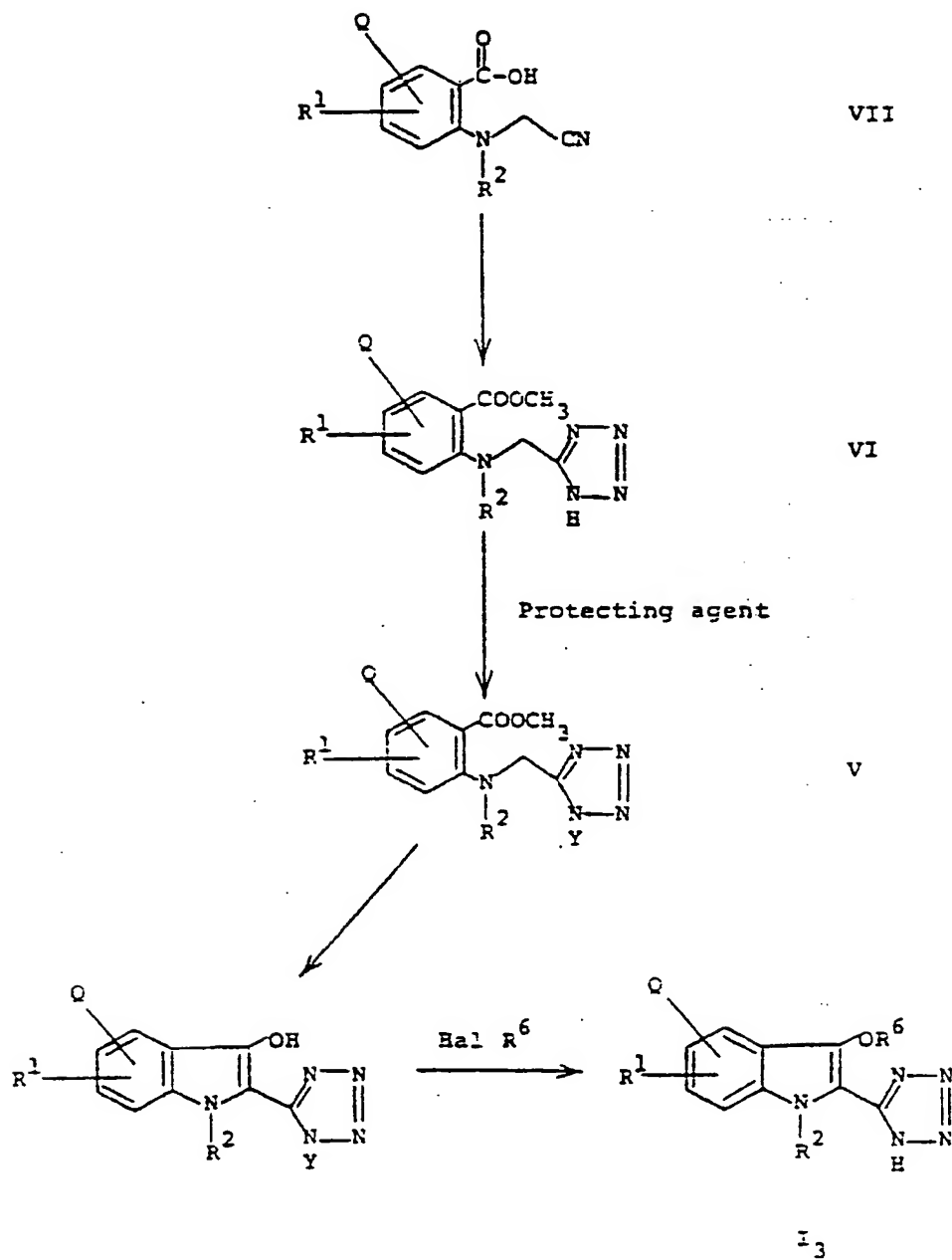
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SCHEME V

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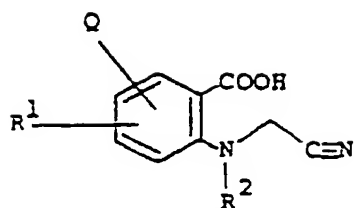
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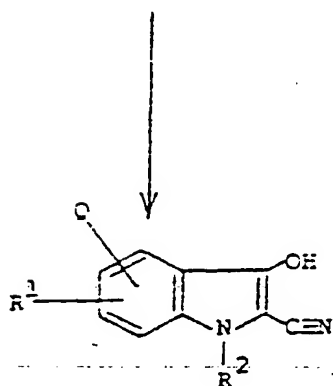
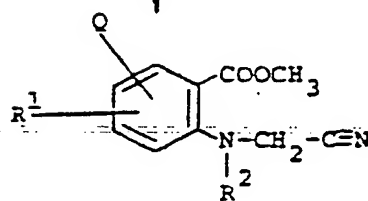
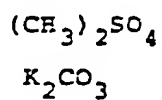
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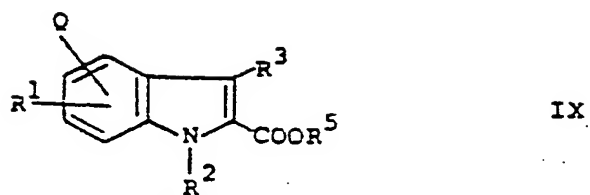


VIII



IV

SCHEME VI



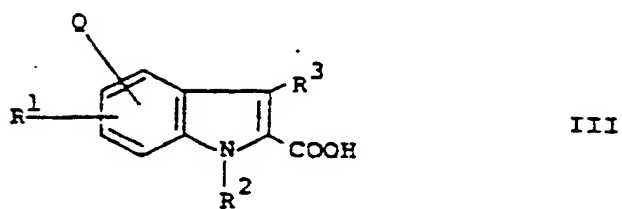
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1) KOH; 2) H⁺

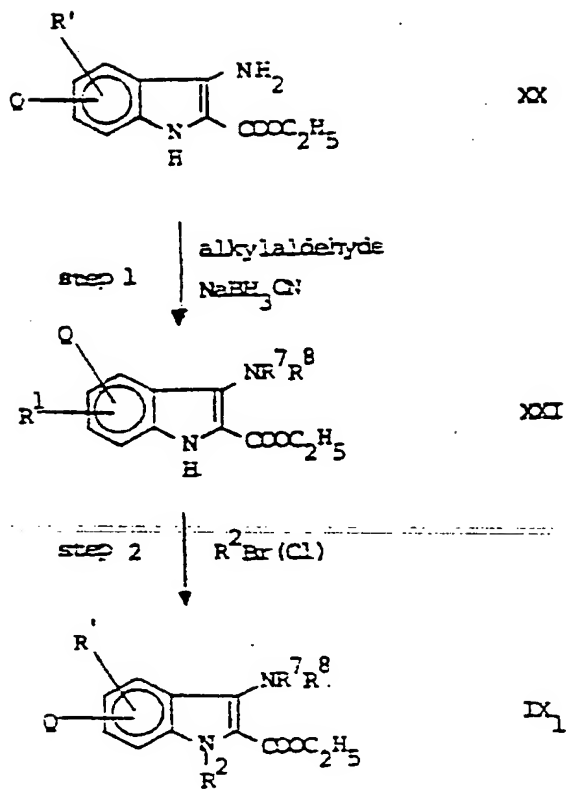
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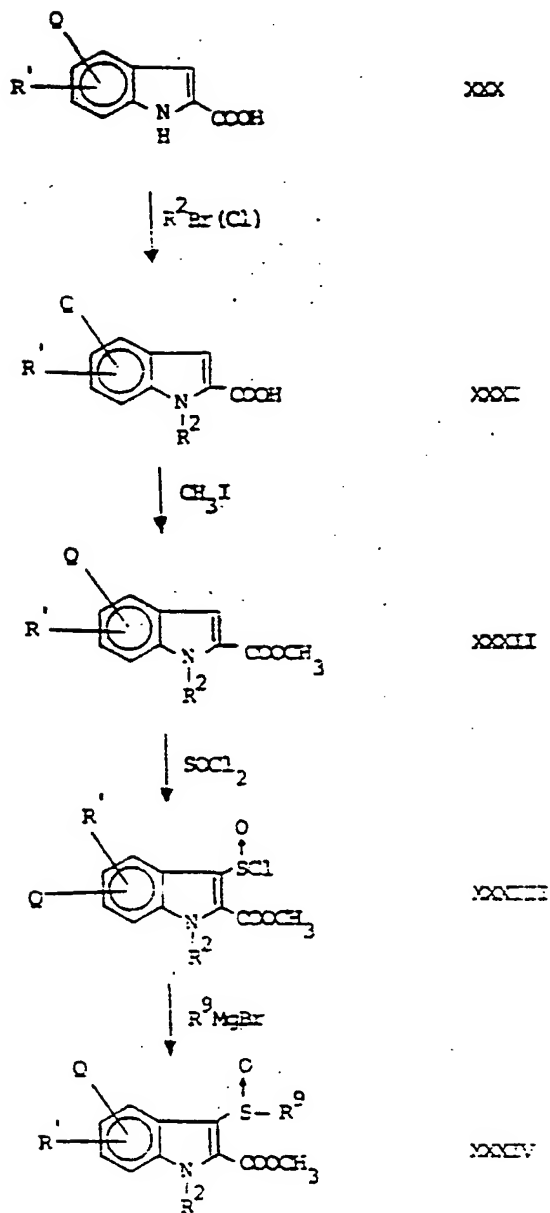
1) KO⁺, DMSO; 2) H⁺



SCHEME VII



SCHEME VIII



SCHEME VII (CONT'D)

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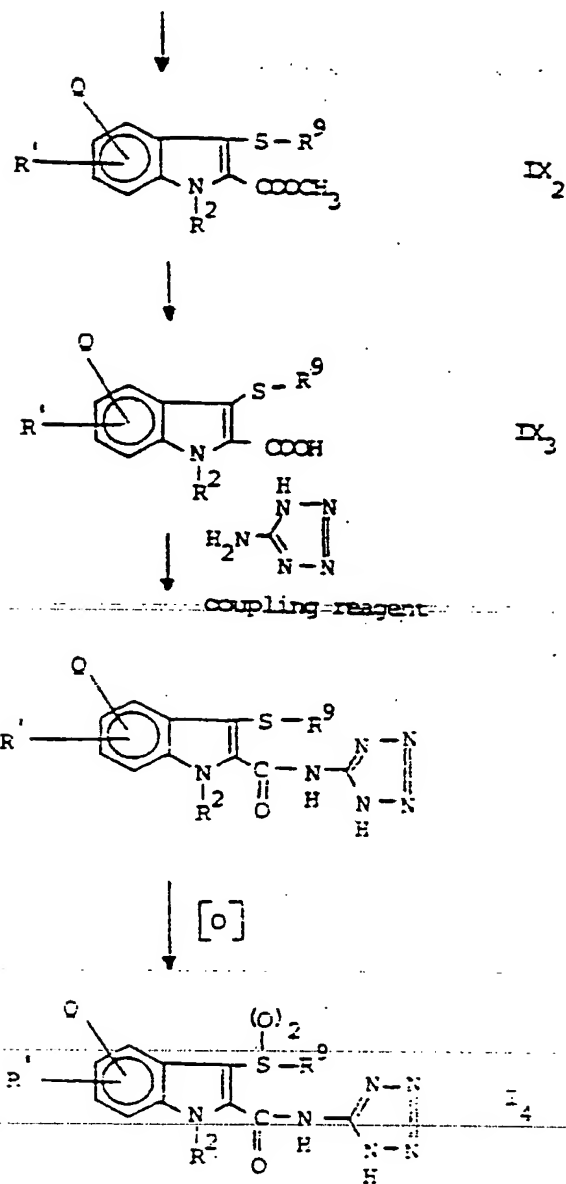
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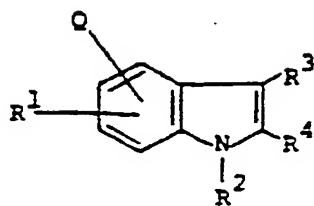
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FORMULA

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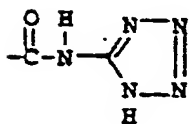
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I

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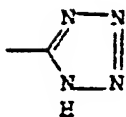


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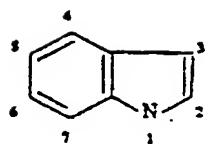
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B

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I¹

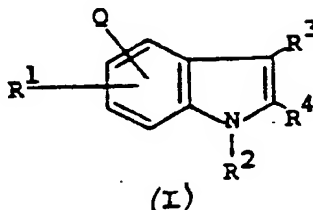
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Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound having the following general formula (I) :



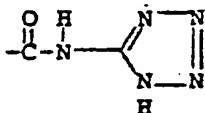
and pharmaceutically acceptable salts thereof, wherein:

R¹ and Q are each, independently, H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, an alkylsulphinyl having from one to four carbon atoms, an alkylsulphonyl having from one to four carbon atoms, a hydroxy group, a nitro group, an amino group, a substituted amino group or a halogen, R¹ being further chosen from a methylenedioxy radical attached to adjacent carbon atoms of the benzene ring;

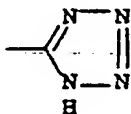
R² is H, an alkyl having from one to twelve carbon atoms, a phenyl radical, a substituted phenyl radical or a benzyl radical;

R³ is H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, a phenylthio radical, a substituted phenylthio radical, an alkylsulphinyl having from one to four carbon atoms, a phenylsulphinyl radical, a substituted phenylsulphinyl radical, an alkylsulphonyl having from one to four carbon atoms, a phenylsulphonyl radical, a substituted phenylsulphonyl radical, an amino group, or a substituted amino group; and

R⁴ is

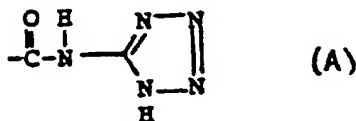


or



[wherein substituted phenyl is a phenyl having one or two substituents selected from alkyl of from one to four carbons inclusive, alkoxy of from one to four carbons inclusive, hydroxy, nitro, amino, mono- or di-alkyl amino wherein alkyl is from one to four carbons, mercapto, alkylthio of from one to four carbons, methylenedioxy, or halogen and substituted amino is mono- or di-alkyl amino wherein alkyl is from one to four carbons.]

2. A compound according to Claim 1, wherein R⁴ is



- 10 3. A compound according to Claim 1, wherein R⁴ is



- 20 4. A compound according to Claim 2, wherein R³ is alkoxy.

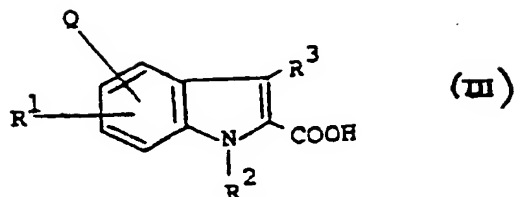
- 25 5. A compound according to Claim 4, having one of the following names:
 3-methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 1-hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-1-(phenylmethyl)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 1-(4-methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-chloro-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 30 5-methoxy-1-methyl-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3,5-dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 35 3-methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
 3-(n-dodecyloxy)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

- 40 6. A compound according to Claim 2 having one of the following names:
 3-(diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-[(1-methylethyl)thio]-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-1-phenyl-3-(phenylthio)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(methylsulphonyl)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
 45 5-methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide

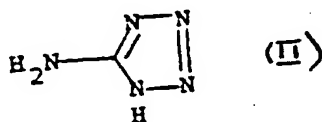
7. A pharmaceutical composition comprising an effective amount of a compound according to any preceding claim in admixture with a pharmaceutically acceptable carrier or diluent.

- 50 8. For use in a method of treating allergies in mammals, a compound as claimed in any one of Claims 1 to 6 or a pharmaceutical composition as claimed in Claim 7.

9. A process for the preparation of a compound of formula I as defined in Claim wherein R⁴ is A, which comprises reacting a compound of the Formula (III)

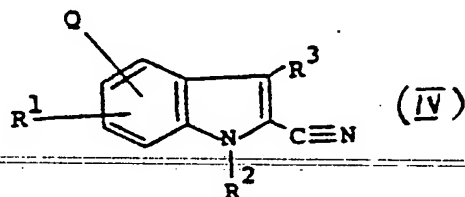


10 wherein R¹, Q, R², and R³ are as defined in Claim 1 with a compound of Formula (II)



in the presence of a coupling agent.

20 10. A process for the preparation of a compound of formula I as defined in Claim 1 wherein R⁴ is B which comprises treating a compound of Formula (IV)



wherein R¹, Q, R², and R³ are as defined in Claim 1 above by a known method or a variant thereof.

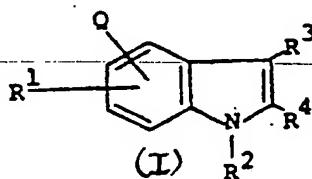
35 11. 5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide, or its L-arginate or sodium salt.

12. 5-Methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

40 13. 1-Phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

Claims for the following Contracting State : AT

45 1. A process for preparing a compound having the following general formula (I) :



55 and pharmaceutically acceptable salts thereof, wherein:

R¹ and Q are each, independently, H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, an alkylsulphonyl having from one to four

carbon atoms, a hydroxy group, a nitro group, an amino group, a substituted amino group or a halogen, R¹ being further chosen from a methylenedioxy radical attached to adjacent carbon atoms of the benzene ring;

R² is H, an alkyl having from one to twelve carbon atoms, a phenyl radical, a substituted phenyl radical or a benzyl radical;

R³ is H, an alkyl having from one to twelve carbon atoms, an alkoxy having from one to twelve carbon atoms, mercapto, an alkylthio having from one to four carbon atoms, a phenylthio radical, a substituted phenylthio radical, an alkylsulphinyl having from one to four carbon atoms, a phenylsulphanyl radical, a substituted phenylsulphanyl radical, an alkylsulphonyl having from one to four carbon atoms, a phenylsulphonyl radical, a substituted phenylsulphonyl radical, an amino group, or a substituted amino group; and

R⁴ is

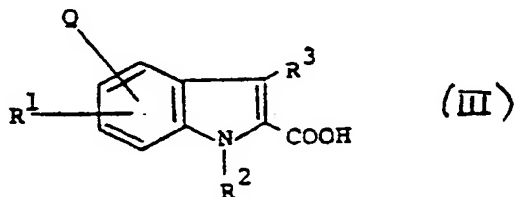


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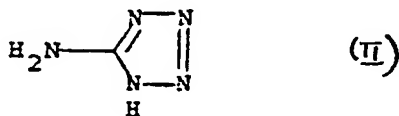


[wherein substituted phenyl is a phenyl having one or two substituents selected from alkyl of from one to four carbons inclusive, alkoxy of from one to four carbons inclusive, hydroxy, nitro, amino, mono- or di-alkyl amino wherein alkyl is from one to four carbons, mercapto, alkylthio of from one to four carbons, methylenedioxy, or halogen and

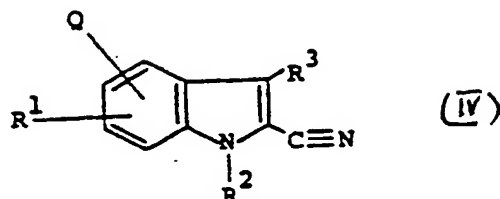
substituted amino is mono- or di-alkyl amino wherein alkyl is from one to four carbons.] which process comprises reacting a compound of the Formula (III)



wherein R¹, Q, R², and R³ are as defined above with a compound of Formula (II)



in the presence of a coupling agent to form a compound of Formula (I) in which R⁴ is A; or treating a compound of formula (IV)



10 wherein R¹, Q, R², and R³, are as defined above by a known method or variant thereof to form a compound of formula (I) in which R⁴ is B; and, if desired, forming a pharmaceutically acceptable salt thereof.

15 2. A process according to Claim 1, wherein R⁴ is



25 3. A process according to Claim 1, wherein R⁴ is



35 4. A process according to Claim 2, wherein R³ is alkoxy.

40 5. A process according to Claim 4, in which one of the following compounds is prepared:

- 3-methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 1-hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-1-(phenylmethyl)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 1-(4-methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-chloro-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-1-methyl-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3,5-dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 3-methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
 3-(n-dodecyloxy)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

55 6. A process according to Claim 2, in which one of the following compounds is prepared:

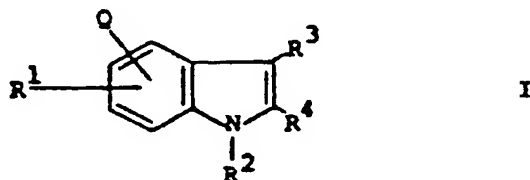
- 3-(diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-[(1-methylethyl)thio]-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-1-phenyl-3-(phenylthio)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide;
 5-methoxy-3-(methylsulphonyl)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide; and
 5-methoxy-3-[(1-methylethyl)thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide.

7. A process for preparing a pharmaceutical composition which process comprises combining an effective amount of a compound prepared in accordance with any preceding claim together with a pharmaceutically acceptable carrier or diluent.
8. For use in a method of treating allergies in mammals, a compound prepared by a process as claimed in any one of Claims 1 to 6 or a pharmaceutical composition prepared by a process as claimed in Claim 7.
9. A process according to claim 1, wherein the following compound is prepared
- 5-methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide or its L-arginate or sodium salt.
10. A process for the preparation of
- 5-methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide or
- 1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indole-2-carboxamide,
- which process comprises reacting a compound of formula III in which Q is hydrogen, R¹ is hydrogen or 5-methoxy, R³ is phenylmethoxy and R² is phenyl with a compound of formula II in the presence of a coupling agent.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der folgenden allgemeinen Formel (I):



und pharmazeutisch annehmbare Salze hiervon, worin:

R¹ und Q jedes für sich, unabhängig voneinander, H, ein Alkyl mit 1 bis 12 Kohlenstoffatomen, ein Alkoxy mit 1 bis 12 Kohlenstoffatomen, Mercapto, ein Alkylthio mit 1 bis 4 Kohlenstoffatomen, ein Alkylsulfinyl mit 1 bis 4 Kohlenstoffatomen, ein Alkylsulfonyl mit 1 bis 4 Kohlenstoffatomen, eine Hydroxygruppe, eine Nitrogruppe, eine Aminogruppe, eine substituierte Aminogruppe oder ein Halogen bedeutet, wobei R¹ weiters ausgewählt ist aus einem Methylendioxyrest, der an die benachbarten Kohlenstoffatome des Benzolrings gebunden ist;

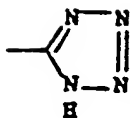
R² H, ein Alkyl mit 1 bis 12 Kohlenstoffatomen, ein Phenylrest, ein substituierter Phenylrest oder ein Benzylrest ist;

R³ für H, ein Alkyl mit 1 bis 12 Kohlenstoffatomen, ein Alkoxy mit 1 bis 12 Kohlenstoffatomen, Mercapto, ein Alkylthio mit 1 bis 4 Kohlenstoffatomen, einen Phenylthio, einen substituierten Phenylthio, ein Alkylsulfinyl mit 1 bis 4 Kohlenstoffatomen, einen Phenylsulfinylrest, einen substituierten Phenylsulfinylrest, ein Alkylsulfonyl mit 1 bis 4 Kohlenstoffatomen, einen Phenylsulfonylrest, einen substituierten Phenylsulfonylrest, eine Aminogruppe oder eine substituierte Aminogruppe steht; und

R⁴ für



oder



(B)

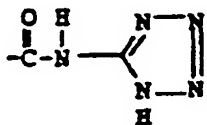
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steht, worin substituiertes Phenyl ein Phenyl mit 1 oder 2 Substituenten, ausgewählt aus Alkyl mit 1 bis einschließlich 4 Kohlenstoffatomen, Alkoxy mit 1 bis einschließlich 4 Kohlenstoffatomen, Hydroxy, Nitro, Amino, Mono- oder Dialkylamino, worin Alkyl 1 bis 4 Kohlenstoffatome aufweist, Mercapto, Alkylthio mit 1 bis 4 Kohlenstoffatomen, Methylendioxy oder Halogen, ist und substituiertes Amino Mono- oder Dialkylamino, worin Alkyl 1 bis 4 Kohlenstoffatome aufweist, ist.

2. Verbindung nach Anspruch 1, worin R⁴

15



(A)

20

ist.

3. Verbindung nach Anspruch 1, worin R⁴

25



(B)

30

ist.

- 35 4. Verbindung nach Anspruch 2, worin R³ für Alkoxy steht.

5. Verbindung nach Anspruch 4, mit einem der folgenden Namen:

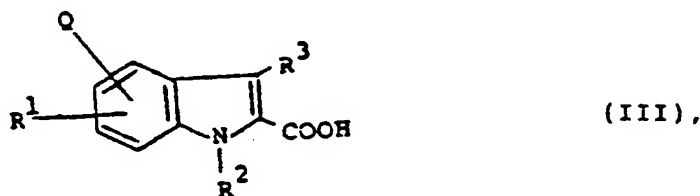
- 3-Methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 1-Hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 40 3-Methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Methoxy-1-(phenylmethyl)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-(1-Methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 1-(4-Methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 45 5-Chlor-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-1-methyl-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3,5-Dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 50 3-Methoxy-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid; und
 3-(n-Dodecyloxy)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid.

- 55 6. Verbindung nach Anspruch 2 mit einem der folgenden Namen:

- 3-(Diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-[(1-methylethyl)-thio]-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;

5-Methoxy-1-phenyl-3-(phenylthio)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
5-Methoxy-3-(methylsulfonyl)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid; und
5-Methoxy-3-[(1-methylethyl)-thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid.

7. Pharmazeutische Zusammensetzung, welche eine wirksame Menge einer Verbindung nach einem der vorhergehenden Ansprüche in Mischung mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel umfaßt.
8. Verwendung einer wie in einem der Ansprüche 1 bis 6 beanspruchten Verbindung oder einer wie im Anspruch 7 beanspruchten pharmazeutischen Zusammensetzung bei einer Methode zur Behandlung von Allergien bei Säugern.
9. Verfahren zu Herstellung einer wie im Anspruch 1 definierten Verbindung der Formel I, worin R⁴ für A steht, welches Verfahren das Umsetzen einer Verbindung der Formel (III)

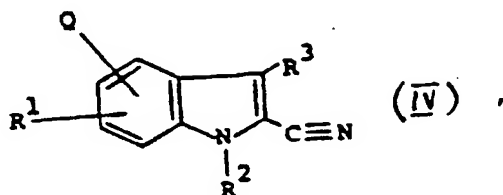


worin R¹, Q, R² und R³ dieselbe Bedeutung wie im Anspruch 1 haben, mit einer Verbindung der Formel (II)



in Gegenwart eines Kopplungsmittels umfaßt.

10. Verfahren zur Herstellung einer wie im Anspruch 1 definierten Verbindung der Formel I, worin R⁴ für B steht, welches das Behandeln einer Verbindung der Formel (IV)

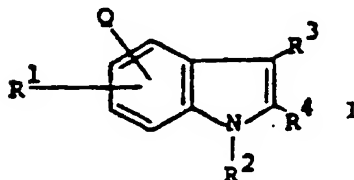


worin R¹, Q, R² und R³ dieselbe Bedeutung wie im Anspruch 1 oben haben, mittels eines bekannten Verfahrens oder einer Variante desselben umfaßt.

11. 5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid oder sein L-Arginat oder Natriumsalz.
12. 5-Methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid.
13. 1-Phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Herstellung einer Verbindung der folgenden allgemeinen Formel (I):



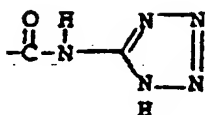
und pharmazeutisch annehmbarer Salze hiervon, worin:

R¹ und Q jedes für sich, unabhängig voneinander, H, ein Alkyl mit 1 bis 12 Kohlenstoffatomen, ein Alkoxy mit 1 bis 12 Kohlenstoffatomen, Mercapto, ein Alkylthio mit 1 bis 4 Kohlenstoffatomen, ein Alkylsulfinyl mit 1 bis 4 Kohlenstoffatomen, ein Alkylsulfonyl mit 1 bis 4 Kohlenstoffatomen, eine Hydroxygruppe, eine Nitrogruppe, eine Aminogruppe, eine substituierte Aminogruppe oder ein Halogen bedeutet, wobei R¹ weiters ausgewählt ist aus einem Methylendioxyrest, der an die benachbarten Kohlenstoffatome des Benzolrings gebunden ist;

R² H, ein Alkyl mit 1 bis 12 Kohlenstoffatomen, ein Phenylrest, ein substituierter Phenylrest oder ein Benzylrest ist;

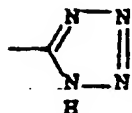
R³ für H, ein Alkyl mit 1 bis 12 Kohlenstoffatomen, ein Alkoxy mit 1 bis 12 Kohlenstoffatomen, Mercapto, ein Alkylthio mit 1 bis 4 Kohlenstoffatomen, einen Phenylthio, einen substituierten Phenylthio, einen Alkylsulfinyl mit 1 bis 4 Kohlenstoffatomen, einen Phenylsulfinylrest, einen substituierten Phenylsulfinylrest, ein Alkylsulfonyl mit 1 bis 4 Kohlenstoffatomen, einen Phenylsulfonylrest, einen substituierten Phenylsulfonylrest, eine Aminogruppe oder eine substituierte Aminogruppe steht; und

R⁴ für



(A)

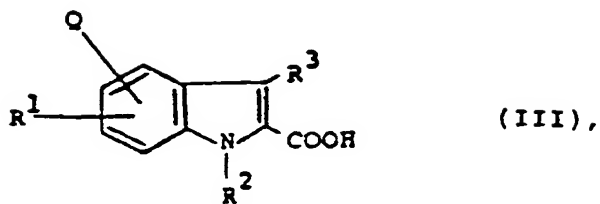
oder



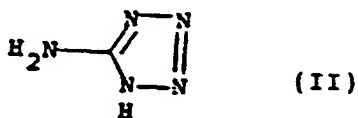
(B),

worin substituiertes Phenyl ein Phenyl mit 1 oder 2 Substituenten, ausgewählt aus Alkyl mit 1 bis einschließlich 4 Kohlenstoffatomen, Alkoxy mit 1 bis einschließlich 4 Kohlenstoffatomen, Hydroxy, Nitro, Amino, Mono- oder Dialkylamino, worin Alkyl 1 bis 4 Kohlenstoffatome aufweist, Mercapto, Alkylthio mit 1 bis 4 Kohlenstoffatomen, Methylendioxy oder Halogen, ist und substituiertes Amino Mono- oder Dialkylamino, worin Alkyl 1 bis 4 Kohlenstoffatome aufweist, ist, steht;

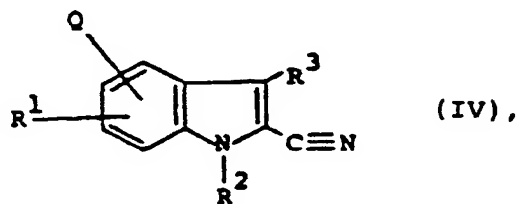
welches Verfahren das Umsetzen einer Verbindung der Formel (III)



10 worin R¹, Q, R² und R³ dieselbe Bedeutung wie oben haben, mit einer Verbindung der Formel (II)



20 in Gegenwart eines Kopplungsmittels, wobei eine Verbindung der Formel (I), worin R⁴ für A steht, gebildet wird; oder das Behandeln einer Verbindung der Formel (IV)



30 worin R¹, Q, R² und R³ die oben angegebene Bedeutung haben, mittels eines bekannten Verfahrens oder einer Variante desselben, wobei eine Verbindung der Formel (I), worin R⁴ für B steht, gebildet wird; und gewünschtenfalls die Bildung eines pharmazeutisch annehmbaren Salzes hievon umfaßt.

35 2. Verfahren nach Anspruch 1, worin R⁴



45 ist.

3. Verfahren nach Anspruch 1, worin R⁴



55 ist.

4. Verfahren nach Anspruch 2, worin R³ für Alkoxy steht.

5. Verfahren nach Anspruch 4, in welchem eine der folgenden Verbindungen hergestellt wird:

3-Methoxy-1-methyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 1-Hexyl-3-methoxy-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indol-carboxamid;
 3-Methoxy-1-(phenylmethyl)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-(1-Methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 1-(4-Methoxyphenyl)-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Chlor-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-1-methyl-3-(1-methylethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3,5-Dimethoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Ethoxy-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Methoxy-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 3-Methoxy-1-nonyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-(n-nonyloxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid; und
 3-(n-Dodecyloxy)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid.

6. Verfahren nach Anspruch 2, in welchem eine der folgenden Verbindungen hergestellt wird:

3-(Diethylamino)-5-methoxy-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-(methylthio)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-[(1-methylethyl)-thio]-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-1-phenyl-3-(phenylthio)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid;
 5-Methoxy-3-(methylsulfonyl)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid; und
 5-Methoxy-3-[(1-methylethyl)-thio]-1-phenylmethyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid.

7. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches Verfahren das Vereinigen einer wirksamen Menge einer Verbindung nach einem der vorhergehenden Ansprüche mit einem pharmazeutisch-annehmbaren Träger oder Verdünnungsmittel umfaßt.

8. Verwendung einer Verbindung, welche mittels eines wie in einem der Ansprüche 1 bis 6 beanspruchten Verfahrens hergestellt wurde, oder einer pharmazeutischen Zusammensetzung, welche mittels eines wie im Anspruch 7 beanspruchten Verfahrens hergestellt wurde, bei einer Methode zur Behandlung von Allergien bei Säugern.

9. Verfahren nach Anspruch 1, worin die folgende Verbindung hergestellt wird:

5-Methoxy-3-(1-methylethoxy)-1-phenyl-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid oder sein L-Arginat oder Natriumsalz.

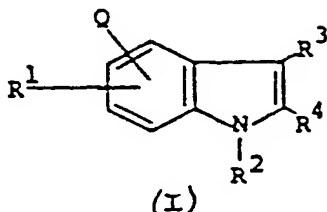
10. Verfahren zur Herstellung von

5-Methoxy-1-phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid oder 1-Phenyl-3-(phenylmethoxy)-N-1H-tetrazol-5-yl-1H-indol-2-carboxamid, welches Verfahren das Umsetzen einer Verbindung der Formel III, worin Q Wasserstoff ist, R¹ Wasserstoff oder 5-Methoxy bedeutet, R³ für Phenylmethoxy steht, und R² Phenyl ist, mit einer Verbindung der Formel II in Gegenwart eines Kopplungsmittels umfaßt.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Un composé de formule générale I:



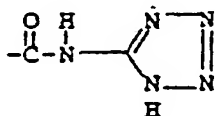
et ses sels pharmaceutiquement acceptables, dans laquelle:

R¹ et Q sont chacun indépendamment un atome d'hydrogène, un radical alkyle ayant de 1 à 12 atomes de carbone, un radical alcoxy ayant de 1 à 12 atomes de carbone, un mercapto, un alkylthio ayant de 1 à 4 atomes de carbone, un alkylsulfinyle ayant de 1 à 4 atomes de carbone, un alkylsulfonyle ayant de 1 à 4 atomes de carbone, un groupe hydroxy, un groupe nitro, un groupe amino, un groupe amino substitué ou un halogène, R¹ pouvant de plus être un radical méthylènedioxy attaché aux atomes de carbone adjacents du cycle benzénique;

R² est un hydrogène, un radical alkyle ayant de 1 à 12 atomes de carbone, un radical phényle, un radical phényle substitué ou un radical benzyle;

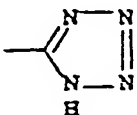
R³ est un hydrogène, un radical alkyle ayant de 1 à 12 atomes de carbone, un radical alcoxy ayant de 1 à 12 atomes de carbone, un mercapto, un alkylthio ayant de 1 à 4 atomes de carbone, un radical phénylthio, un radical phénylthio substitué, un alkylsulfinyle ayant de 1 à 4 atomes de carbone, un radical phénylsulfinyle, un radical phénylsulfonyle substitué, un radical alkylsulfonyle ayant de 1 à 4 atomes de carbone, un radical phénylsulfonyle, un radical phénylsulfonyle substitué, un groupe amino ou un groupe amino substitué; et

R⁴ est R³ is



(A)

où

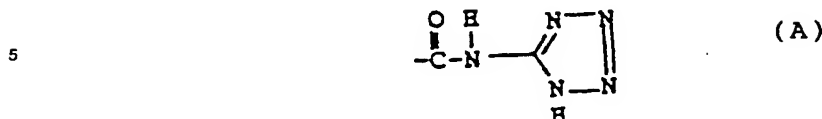


(B)

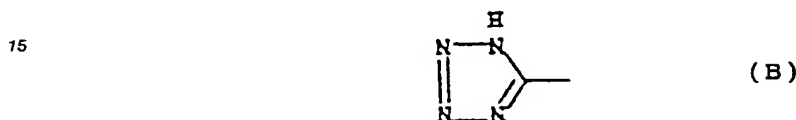
où

le radical phényle substitué est un phényle ayant 1 ou 2 substituants choisis parmi les groupes suivants: alkyle de 1 à 4 atomes de carbone, bornes comprises, alcoxy de 1 à 4 atomes de carbone, bornes comprises, hydroxy, nitro, amino, mono- ou dialkylamino dans lequel le groupe alkyle contient de 1 à 4 atomes de carbone, mercapto, alkylthio de 1 à 4 atomes de carbone, méthylènedioxy, ou halogène, et le groupe amino substitué est un mono ou dialkylamino dans lequel l'alkyle contient de 1 à 4 atomes de carbone.

2. Un composé selon la revendication 1, dans lequel R⁴ est:



- 10
3. Un composé selon la revendication 1, dans lequel R⁴ est:



- 20
4. Un composé selon la revendication 2, dans lequel R³ est un alcoxy.

5. Un composé selon la revendication 4, ayant l'un des noms suivants:

25 3-méthoxy-1-méthyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
1-hexyl-3-méthoxy-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-1-nonyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-1-(phénylméthyl)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
30 1-(4-méthoxyphényl)-3-(1-méthyléthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-chloro-3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-1-méthyl-3-(1-méthyléthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3,5-diméthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-éthoxy-5-méthoxy-2-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
35 5-méthoxy-3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-1-nonyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-3-(n-nonyloxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide, et
3-(n-dodécyloxy)-5-méthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide.

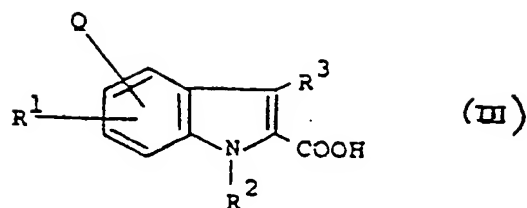
- 40
6. Un composé selon la revendication 2, ayant un des noms suivants:

3-(diéthylamino)-5-méthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide;
5-méthoxy-3-(méthylthio)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide;
5-méthoxy-3-[(1-méthyléthyl)thio]-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
45 5-méthoxy-1-phényl-3-(phénylthio)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-3-(méthylsulfonyl)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide, et
5-méthoxy-3-[(1-méthyléthyl)thio]-1-phénylméthyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide.

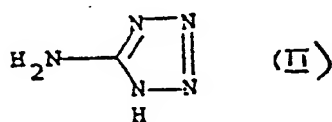
- 50
7. Une composition pharmaceutique comprenant une quantité efficace d'un composé selon l'une quelconque des revendications précédentes, mélangé à un support ou diluant pharmaceutiquement acceptable.

8. Un composé selon l'une quelconque des revendications 1 à 6, ou une composition pharmaceutique selon la revendication 7, destiné à être utilisé pour le traitement des allergies mammifères.

- 55
9. Un procédé de préparation d'un composé de formule I tel que défini dans la revendication 1, dans lequel R⁴ est A, lequel procédé consiste à faire réagir un composé de formule III

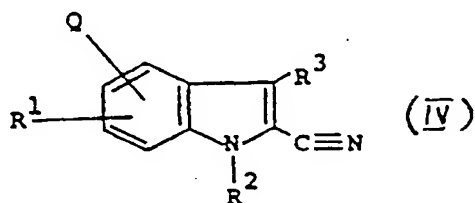


10 dans laquelle R¹, Q, R² et R³ sont tels que définis dans la revendication 1, avec un composé de formule II



20 en présence d'un agent de couplage.

- 25 10. Un procédé de préparation d'un composé de formule I tel que défini dans la revendication 1, dans laquelle R⁴ est B, lequel procédé consiste à traiter un composé de formule IV

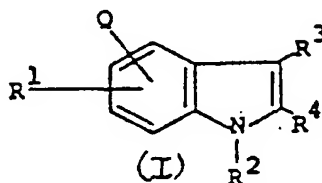


35 dans laquelle R¹, Q, R² et R³ sont tels que définis dans la revendication 1 ci-dessus, par un procédé connu ou une variante d'un tel procédé.

- 40 11. 5-méthoxy-3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide, ou son dérivé L-arginate ou sel de sodium.
- 45 12. 5-méthoxy-1-phényl-3-(phénylméthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide.
- 50 13. 1-phényl-3-(phénylméthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide.
- 55

Revendications pour l'Etat contractant suivant : AT

1. Un procédé de préparation d'un composé de formule générale suivante I:



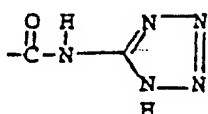
et ses sels pharmaceutiquement acceptables, dans laquelle:

R¹ et Q sont chacun indépendamment un atome d'hydrogène, un radical alkyle ayant de 1 à 12 atomes de carbone, un radical alcoxy ayant de 1 à 12 atomes de carbone, un mercapto, un alkylthio ayant de 1 à 4 atomes de carbone, un alkylsulfinyle ayant de 1 à 4 atomes de carbone, un alkylsulfonyl ayant de 1 à 4 atomes de carbone, un groupe hydroxy, un groupe nitro, un groupe amino, un groupe amino substitué ou un halogène, R¹ pouvant de plus être un radical méthylènedioxy attaché aux atomes de carbone adjacents du cycle benzénique;

R² est un hydrogène, un radical alkyle ayant de 1 à 12 atomes de carbone, un radical phényle, un radical phényle substitué ou un radical benzyle;

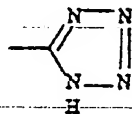
R³ est un hydrogène, un radical alkyle ayant de 1 à 12 atomes de carbone, un radical alcoxy ayant de 1 à 12 atomes de carbone, un mercapto, un alkylthio ayant de 1 à 4 atomes de carbone, un radical phénylthio, un radical phénylthio substitué, un alkylsulfinyle ayant de 1 à 4 atomes de carbone, un radical phénylsulfinyle, un radical phénylsulfonyl substitué, un radical alkylsulfonyl ayant de 1 à 4 atomes de carbone, un radical phénylsulfonyl, un radical phénylsulfonyl substitué, un groupe amino ou un groupe amino substitué; et

R⁴ est R³ is



(A)

où

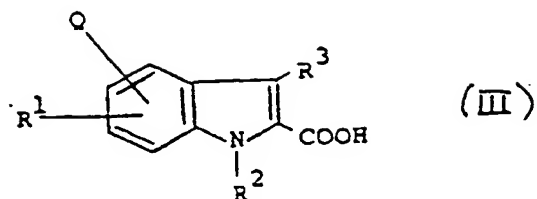


(B)

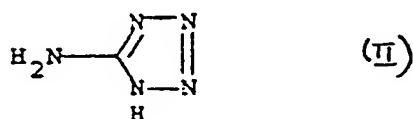
où

le radical phényle substitué est un phényle ayant 1 ou 2 substituants choisis parmi les groupes suivants: alkyle de 1 à 4 atomes de carbone, bornes comprises, alcoxy de 1 à 4 atomes de carbone, bornes comprises, hydroxy, nitro, amino, mono- ou dialkylamino dans lequel le groupe alkyle contient de 1 à 4 atomes de carbone, mercapto, alkylthio de 1 à 4 atomes de carbone, méthylènedioxy, ou halogène, et le groupe amino substitué est un mono ou dialkylamino dans lequel l'alkyle contient de 1 à 4 atomes de carbone,

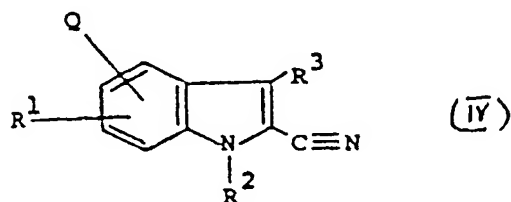
lequel procédé consiste à faire réagir un composé de formule III:



10 dans laquelle R¹, Q, R² et R³ sont tels que définis ci-dessus, avec un composé de formule II:

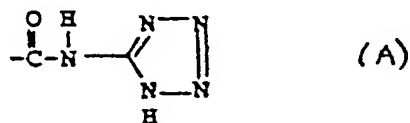


20 en présence d'un agent de couplage afin de former un composé de formule I dans laquelle R⁴ est A, ou
à traiter un composé de formule IV:



35 dans laquelle R¹, Q, R² et R³ sont tels que définis par un procédé connu ou une de ses variantes pour former un composé de formule I dans laquelle R⁴ est B; et, si désiré, à former un de ses sels pharmaceutiquement acceptable.

2. Un procédé selon la revendication 1, dans lequel R⁴ est:



3. Un procédé selon la revendication 1, dans lequel R⁴ est:



4. Un procédé selon la revendication 2, dans lequel R³ est un alcoxy.

5. Un procédé selon la revendication 4, dans lequel un des composés suivants est préparé:
3-méthoxy-1-méthyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
1-hexyl-3-méthoxy-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-1-nonyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5 3-méthoxy-1-(phénylméthyl)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
1-(4-méthoxyphényl)-3-(1-méthyléthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-chloro-3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
10 5-méthoxy-1-méthyl-3-(1-méthyléthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3,5-diméthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-éthoxy-5-méthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
3-méthoxy-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
15 3-méthoxy-1-nonyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-3-(n-nonyloxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide, et
3-(n-dodécyloxy)-5-méthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide.
6. Un procédé selon la revendication 2, dans lequel l'un des composés suivants est préparé:
20 3-(diéthylamino)-5-méthoxy-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide;
5-méthoxy-3-(méthylthio)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-3-[(1-méthyléthyl)thio]-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-1-phényl-3-(phénylthio)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
5-méthoxy-3-(méthylsulfonyl)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide, et
25 5-méthoxy-3-[(1-méthyléthyl)thio]-1-phénylméthyl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide.
7. Un procédé de préparation d'une composition pharmaceutique, lequel procédé consiste à combiner une quantité efficace d'un composé préparé selon l'une quelconque des revendications précédentes, avec un support ou diluant pharmaceutiquement acceptable.
8. Un composé préparé par un procédé tel que revendiqué dans l'une des revendications 1 à 6, ou une composition pharmaceutique préparée par un procédé tel que revendiqué dans la revendication 7, pour l'utilisation pour le traitement des allergies.
9. Un procédé selon la revendication 1, dans lequel est préparé le composé suivant: 5-méthoxy-3-(1-méthyléthoxy)-1-phényl-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide, ou son dérivé L-arginate ou sel de sodium.
10. Un procédé de préparation du 5-méthoxy-1-phényl-3-(phénylméthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
40 ou du 1-phényl-3-(phénylméthoxy)-N-1H-tétrazol-5-yl-1H-indole-2-carboxamide,
lequel procédé consiste à faire réagir un composé de formule III dans laquelle Q est un hydrogène, R¹ est un hydrogène ou un 5-méthoxy, R³ est un phénylméthoxy et R² est un groupe phényle, avec un composé de formule II en présence d'un agent de couplage.

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